



Research Article

Formulation, Development and Evaluation of Sildenafil Citrate Oral Jelly

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Abstract

Background: The site of drug administration, such as oral or intravenous, frequently categorizes the route of administration. Drug delivery through oral jelly reduces product costs and enhances product stability and appearance. Oral jelly is used as a drug carrier for different diseases like erectile dysfunction, arthritis, hypertension, and sore throats. Medicated jelly is easy to administer at any time and place without water. **Aim:** To formulate, develop, and evaluate sildenafil citrate oral jelly. **Methods:** Oral jelly formulations (F1–F5) with different amounts of excipients and sildenafil citrate were made and tested for things like pH, appearance, viscosity, and drug release in a test tube. The data were analyzed by SPSS version 25 software. **Results:** The pre-formulation FTIR study revealed that there was no significant interaction between the drug and the excipients used. The pH of all of the formulations was within the desirable range (6.3-6.8), indicating their suitability for product stability and patient acceptability. The stability study indicated that during one-month storage at 25° C and at 40° C/ 75% RH, no significant changes in the properties of the product were found. The viscosity of the formulations increased with increasing sodium CMC concentrations. The HPLC-based in-vitro drug release study indicated that the best drug release was achieved in the F5 formulation. **Conclusion:** It was concluded that F5 is the formulation of choice satisfying the ideal characteristics of an oral jelly formulation with an improvement in the drug bioavailability over the existing marketed oral formulations of Sildenafil.

Keywords: Sildenafil, Jelly, Spreadability, Extrudability, pH, Stability

صياغة وتطوير وتقييم سيلدينافيل سترات هلام الفم

الخلاصة

الخلفية: يصنف موقع إعطاء الدواء، مثل الفم أو الوريد، بشكل طريق الإعطاء. توصيل الدواء عن طريق الفم يقلل من تكاليف المنتج ويعزز استقرار المنتج ومظهره. يستخدم هلام الفم كحامل للأدوية لأمراض مختلفة مثل ضعف الانتصاب والتهاب المفاصل وارتفاع ضغط الدم والتهاب الحلق. من السهل إعطاء الهلام الطبي في أي وقت ومكان بدون ماء. **الهدف:** صياغة وتطوير وتقييم هلام الفم سترات السيلدينافيل. **الطرق:** تم تصنيع تركيبات الهلام عن طريق الفم (F1-F5) بكميات مختلفة من السواغات وسترات السيلدينافيل واختبارها بحثًا عن أشياء مثل الأس الهيدروجيني والمظهر واللزوجة وإطلاق الدواء في أنبوب اختبار. تم تحليل البيانات بواسطة برنامج SPSS الإصدار 25. **النتائج:** كشفت دراسة FTIR قبل الصياغة أنه لا يوجد تفاعل كبير بين الدواء والسواغات المستخدمة. كان الرقم الهيدروجيني لجميع التركيبات ضمن النطاق المرغوب فيه (6.3-6.8)، مما يشير إلى ملاءمتها لاستقرار المنتج وقبول المريض. أشارت دراسة الثبات إلى أنه خلال التخزين لمدة شهر واحد عند 25 درجة مئوية وعند 40 درجة مئوية/ 75% رطوبة نسبية، لم يتم العثور على تغييرات كبيرة في خصائص المنتج. زادت لزوجة التركيبات مع زيادة تركيزات CMC الصوديوم. أشارت دراسة إطلاق الدواء في المختبر المستندة إلى HPLC إلى أنه تم تحقيق أفضل إطلاق للدواء في تركيبة F5. **الاستنتاج:** استنتج أن F5 هي الصيغة المفضلة التي تلبى الخصائص المثالية لصياغة هلام الفم مع تحسين التوافر البيولوجي للدواء على التركيبات الفموية الحالية المسوقة من السيلدينافيل.

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INTRODUCTION

The location of drug administration, such as oral or intravenous, frequently serves to categorize the route of administration. This choice depends not only on the pharmacokinetics and pharmacodynamics of the drug but also on patient acceptability. A successful dosage form in drug therapy is the one that immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constantly for the entire duration of treatment [1]. Additionally, it should be convenient to administer. Many types of advanced dosage forms are on the market, but conventional pharmaceutical dosage forms are still dominant. Among these formulations, oral delivery forms are the most popular because they are usually easy to administer and available at a relatively low cost [2]. In the case of tablets, many functional excipients are needed to modify the release of the drug from the dosage form; additionally, it may impose difficulties in swallowing for certain patients. The throats of patients suffering from dysphagia can get choked while consuming watery liquid formulations; however, this difficulty can be eliminated by administering high viscous liquid formulations with jelly [3]. Drug delivery through oral jelly reduces product costs and enhances product stability and appearance. Different types of drugs can also be incorporated into them and dissolved in the oral cavity for local or systemic effects. Oral jelly can be used as a drug carrier for different diseases like erectile dysfunction, arthritis, antihypertensive, sore throat, and so on [4]. Patients suffering from Parkinson's disease for whom chewing is difficult and painful or whose lower jaw is paralyzed can administer medicated jelly easily. In addition to higher patient compliance and good rheological behavior, oral jelly has the suitability of being administered at any time and place without the requirement of water [5]. The main constraints of oral jelly are the side effects such as flatulence and diarrhea that might result from the presence of sucrose and sorbitol, the possibility of an unpleasant mouthfeel, and the requirement of special packaging due to its high moisture content [6]. Additionally, as they are prepared in a hydrated form containing a large proportion of water, that may cause instability issues for certain drugs and hence require antimicrobial preservatives. Thus, to overcome such drawbacks, an attempt was made to develop a viscous and stable oral jelly formulation containing Sildenafil Citrate (20 mg). In this work, various prototype formulations were prepared and evaluated concerning their physical characteristics in terms of viscosity, pre-formulation parameters, dissolution, assay, and stability [7]. Sildenafil citrate was taken as a model drug, and jelly was designed to be dissolved in the mouth, not swallowed [8].

METHODS

Chemicals and Reagents

Pharmaceutical-grade Sildenafil citrate (99%) was procured from Dr. Reddy's Pharma Ltd., Hyderabad, India. HPLC-grade ammonium acetate and acetonitrile were used for the preparation of the mobile phase. The rest of the chemicals of analytical grade were procured from local sources.

Formulation Development and Evaluation

An infrared spectrophotometer (JASCO, Japan) was used for recording spectra in the region of 4000–650 to study the drug-excipient interactions. Approximately 1-2 mg of the powder was mixed and triturated with 100 mg of dried potassium bromide reagent; the pellet was made with the mixture powder by direct compression.

Preparation of oral jelly

A total of five batches of formulation were prepared with different compositions of ingredients listed in Table 1. Sodium carboxymethylcellulose was dissolved in glycerin and kept for 24 hours.

Table 1: Formulation of Sildenafil Citrate

Ingredients	F1	F2	F3	F4	F5
Sildenafil Citrate (gm)	2.0	2.0	2.0	2.0	2.0
Sodium CMC (gm)	1	1.1	1.15	1.2	1.3
Glycerin (ml)	50	50	50	50	50
Talc (gm)	0.5	0.5	0.5	0.5	0.5
Sodium Benzoate (gm)	0.075	0.085	0.09	0.095	0.1
Saccharin Sodium (gm)	3.2	3.1	2.85	2.9	3.0
Flavor strawberry (ml)	1.25	1.45	1.3	1.4	1.5
Colour Erythrosine supra (gm)	0.085	0.075	0.04	0.015	0.01
Distilled water	q.s	q.s	q.s	q.s	q.s

Additionally, Sildenafil Citrate was added to it and mixed until a homogenous mixture was formed. The remaining excipients (talc, sodium benzoate, and saccharin sodium) were then added to the formulation, followed by milling. Thereafter, the products were stored for further studies.

Rheological study

The rheological characteristics of the jelly were studied using a Brookfield DV 2+Pro viscometer (Brookfield Engineering, USA) equipped with a small sample adapter and a spindle with no S-31. 10 ml of sample was taken in the adapter and subjected to shear rates in the 10 to 100 sec⁻¹ range. All measurements were carried out at 25°C ±0.5°C. The results are then reported as the mean of six determinations [9].

Determination of drug content

Uniformity of content was performed by dissolving the jelly formulation containing 20mg of drug in a 100-ml volumetric flask, followed by filtration through a 0.45 µm filter. After proper dilution, it was subjected to analysis [10,11]. The amount of drug

content in the formulation was determined by the HPLC method. The Agilent 1600 HPLC system with a C18 column of 250×4.5mm diameter with a 5µm pore size was used. The flow rate was kept at 0.5ml/min at a column temperature of 25°C. The mobile system was constituted by taking 0.02 M ammonium acetate and acetonitrile in a ratio of 50:50 with an injection volume of 10 µL. The wavelength of the detector was fixed at 245 nm.

In vitro drug release study

The jelly containing 20mg of drug was placed inside the basket of the dissolution apparatus containing a dissolution medium of 900 ml of 0.01N HCl equilibrate to 37±0.5°C at a speed of 100 rpm for 30 min. 10 ml of sample was withdrawn from the vessel and filtered through a 0.45 µm nylon filter [12,13]. Then the drug content was determined by the HPLC method as described above. HPLC columns were washed and equilibrated with the mobile phase. 10 µL of samples were injected separately into the chromatographic system. The peak obtained for Sildenafil citrate oral jelly was recorded accordingly. The percentage of drug content was calculated using the following formula:

$$\left[\frac{A_T}{A_S} \times \left(\frac{W_{std}}{25} \right) \times \left(\frac{1}{10} \right) \times \left(\frac{1000}{L} \right) \times \left(\frac{P}{100} \right) \right] \times 100$$

Where, A_T = Area of Sildenafil citrate oral jelly (from test preparation)

A_S = Average area counts of Sildenafil citrate (from standard preparation)

Wed = Weight of the Sildenafil citrate (mg)

P = % Potency of Sildenafil citrate

L = Label claim of Sildenafil citrate oral jelly (mg)

Stability study

Generally, the pH affects the stability and taste of the dosage form. Thus, it is necessary to measure the pH of the formulation to ensure its stability. In our study, a digital pH meter (Systronics) was used for pH measurement. The electrode was inserted into the jelly for 10 minutes to get stable pH data at room temperature [14]. The stability evaluation of the prepared formulations was carried out for 4 weeks at 25°C and 40°C with 75% RH, kept in glass vials sealed with low-density polyethylene (LDPE) plugs that were punctured to ensure moisture permeation. The change in pH, general appearance, viscosity, and drug content were noted.

RESULTS AND DISCUSSION

The oral jelly of sildenafil citrate is prepared by simple incorporation and mixing methods. Drug-excipient interactions were investigated by FTIR in the pre-formulation study. The FTIR results of Sildenafil citrate showed a peak in the 3000–3300 cm^{-1} region, which demonstrated the secondary

amide vibrations (N–H stretching). The peak found in the 1500–1400 cm^{-1} region is due to vibrations of the aromatic rings (C–C stretching). C–H deformations were observed due to the weak bands at 1200–1000 cm^{-1} . The band at 3665 cm^{-1} clearly confirmed the O–H stretching of the hydrated form. Furthermore, a pre-formulation study of Sildenafil citrate with all major excipients like sodium CMC, sodium saccharine, sodium benzoate, and talcum was performed separately. The compatibility results revealed that no interaction was found between the drug and the excipient. The rheological study indicates that all the jelly formulations have a non-Newtonian type of flow. Table 2 demonstrates the content uniformity results. The pH of the formulations, which is a major cause of stability and the patient's acceptance of administration in the oral cavity, was found to be within the range of 6.3–6.8.

Table 2: Physicochemical characterization of Sildenafil Citrate

Formula	pH	Drug content (%)	Viscosity (Cps)
F1	6.3±0.32	98.25±2.25	11047±50
F2	6.0±0.56	98.75±3.36	12415±70
F3	6.2±0.38	97.52±2.36	15442±63
F4	6.5±0.48	97.36±2.39	18101±52
F5	6.8±0.25	99.35±3.65	23105±62

The percentage of drug content in all of the formulations was within 98.25–99.35%, indicating the uniform distribution of the drug as it is present within the acceptable level of 90%–110%. The F5 formulation had the optimum viscosity desirable for a jelly formulation [15]. The quantitative determination of drug content was determined by the HPLC method. The composition of the mobile phase was found to be optimal for a good peak shape as well as achieving minimal background current. A typical chromatogram for the estimation of Sildenafil citrate was obtained by using the aforementioned mobile phase of the assay preparation (Figure 1).

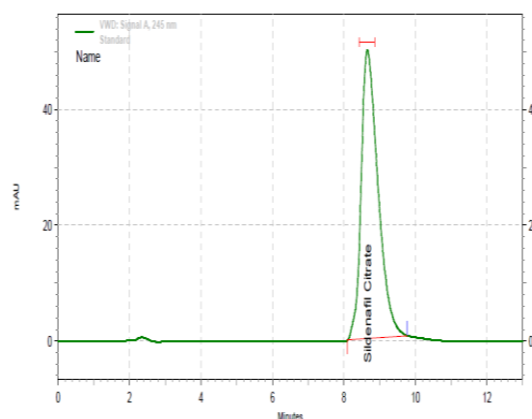


Figure 1: HPLC Chromatogram of sildenafil citrate.

In-vitro dissolution profile of Sildenafil citrate oral jelly was evaluated by HPLC, and the percentage of cumulative drug release was found to be highest in F5 (Table 3).

The study showed that F5 released more than 99% of the drug within 30 minutes of the test. The results from the stability study (Table 4) indicated no significant changes in pH or appearance in all the formulations with time. In the case of viscosity, a decrease was observed at 40°C which might be contributed by the higher temperature. Therefore, it is recommended that 25°C is the best temperature to store the prepared jelly.

Table 4: Stability parameters at different conditions

Formula	Storage conditions (After 4 weeks)							
	25°C temperature				40° C at 75 % of relative humidity			
	General appearance	pH	Viscosity (CpS)	Drug conc. (%)	General appearance	pH	Viscosity (CpS)	Drug conc. (%)
F1	No change	6.3±0.32	1104±50	98.25±2.25	No change	6.2±0.42	1052±75	98.20±2.32
F2	No change	6.0±0.56	1241±70	98.75±3.36	No change	6.1±0.50	1212±50	98.18±2.41
F3	No change	6.2±0.38	1544±63	97.52±2.36	No change	6.3±0.48	1502±60	97.95±2.25
F4	No change	6.5±0.48	1810±52	97.36±2.39	No change	6.4±0.44	1802±63	97.25±2.25
F5	No change	6.8±0.25	2310±62	99.35±3.65	No change	6.7±0.35	2225±69	99.25±3.25

Conclusion

The present work demonstrates the successful development of a new formulation "Oral Jelly Formulation of Sildenafil Citrate". Five prototype formulations were designed, and their physicochemical properties were studied and optimized to get a satisfactory formula. It is concluded that the F5 formulation came up as the best formulation with ideal characteristics such as pH, assay, viscosity, and dissolution profile. From a stability point of view, there was no significant behavioral change in all the prototype formulations within 4 weeks of study. These results are very encouraging for future marketing of oral jelly formulations, replacing the currently predominant conventional oral dosage forms.

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Conflicts of interest

There are no conflicts of interest.

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

Table 3: Percentage of cumulative drug release

Time (min)	Percentage cumulative drug released				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	52.05	60.26	65.65	71.35	78.25
10	62.25	70.25	72.65	76.65	89.25
15	70.25	80.25	85.26	89.69	94.2
30	79.25	85.36	92.65	95.36	99.92

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