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Research Article

Extemporaneous preparation of paediatric oral formulations with sildenafil citrate

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Abstract

The paediatric population is composed of several very different subgroups, each with its own specific characteristics. For this reason, children cannot be considered "small adults". The development of formulations suitable for children is a complex process, as it must consider the physiological changes that occur during childhood and the impact they have on the absorption of drugs. Sildenafil citrate is a drug with a narrow therapeutic index used in paediatrics to treat pulmonary hypertension. In the present work, technological approaches for extemporaneous preparation of paediatric oral forms containing sildenafil citrate for personalized therapy in children were studied. The prepared formulations were tested for physical and microbiological stability, in-use stability, and determination of active substance content. All tested oral formulations remained unchanged in terms of appearance during the entire period of stability monitoring at the selected storage conditions – room temperature 25 °C ± 5 °C and in a refrigerator at 5 °C ± 2 °C. The established pH values suggest that the formulations remained chemically stable during the stability study. The content of sildenafil citrate in all prepared oral formulations remained above 95% w/v. The microbiological quality of the prepared compositions was confirmed. Rational strategies for preparation of extemporaneous formulations were proposed based on the analysis of experimental data.

Keywords

sildenafil, extemporaneous drug dosage forms, oral suspensions, paediatric oral dosage forms, personalized therapy

Introduction

Children make up almost 21% of the European population, or over 100 million people. The paediatric population is composed of several very different subgroups, namely: newborns (0–1 month), infants (1 month–2 years), children (2–12 years) and adolescents (12–16 years) (FDA Guidance for industry 1998). Each of these subgroups has its own specific characteristics, that is why children cannot be considered "small adults" (Fernandez et al. 2011; Soroceanu et al. 2013). The individual groups differ in many aspects such as physical development, pharmacokinetics, and pharmacodynamics. Newborns are characterized by underdeveloped drug-metabolizing enzyme systems and renal function. The distribution of drugs in newborns is different due to the high-water content – 80%, while the adult organism is composed of 55–60% water. Also, the permeability of the blood-brain barrier in children is higher than in adults. Newborns have slower gastrointestinal passage, but faster muscle resorption associated with limited protein content. Small children often have two to three times longer drug elimination half-life compared to adults, which requires lower drug doses (Ginsberg et al. 2002; Alcorn and McNamara 2003; Lu and Rosenbaum 2014). In addition, the child's organism is constantly evolving. In the process of transforming a child into an

adult, the child's body overpasses certain stages and periods, which are characterized by changes in its morphological and physiological characteristics. Also, the pathophysiology of some diseases and pharmacological receptor functions changes in childhood and differ from those in adults. For example, most cases of hypertension in children are secondary due to kidney disease, while most cases of hypertension in adults are primary (Benjamin 2008). Therefore, even when the drug has a well-established effect in adults, the linear dose/kg relationship often cannot be applied to children. Considering these facts, it is clear that the dosage regimen in children cannot simply be extrapolated from adults, and effective therapy requires drugs to be specifically adapted to the children`s needs. The development of formulations suitable for children is a complex process, as it must consider the physiological changes that occur during childhood and the impact they have on the absorption of drugs. Drug dosage forms used in paediatric pharmacotherapy should be adapted so that to meet all requirements, age, size, physiological state (Rieder 2010; Turner 2011; Tuleu and Breitkreutz 2013). The lack of information about the use of most drugs for children is one of the main problems in the development of paediatric drug dosage forms. There is often a need for personalized drug doses or choice of an alternative route of administration or pharmaceutical form in routine paediatric practice. Despite efforts at European and national level, only around 20% of the formulations available on the market are approved for paediatric use. The use of unlicensed drugs for children or the so-called off-label therapy, is widespread, which has caused various problems in recent years because these medicinal products contain different types and amounts of excipients, which may not be safe for children and are not approved for paediatric use (Allen et al. 2018). Another major problem is related to the dose regimen of paediatric dosage forms. The medicinal products for children must assure measuring of very low doses and their easy application, precise and rational selection of excipients, attractive packaging, etc. The medicines for paediatric patients should be dosed in mg/kg or mg/m^2.

Most medicines taken by children are prepared extemporaneously by a pharmacist, so there is no information about bioavailability, suitability, stability, and safety. This is due to the fact that the possibilities to control the quality of these medicines in the pharmacy are quite limited, in terms of the available equipment for analysis. In routine pharmaceutical practice, the extemporaneous preparation of the appropriate paediatric dosage form can be done either by using an active pharmaceutical ingredient (API) or by handling commercially available marketed drug products. It must be noted that it is recommended these extemporaneous formulations to be prepared from an API, if available (Choonara and Conroy 2002; Neubert et al. 2004; Mason et al. 2012; Bellis et al. 2013; Cuzzolin 2014; Magalhaes et al. 2014; Bjerknes 2017; Richey et al. 2017; Roque 2017; Binson et al. 2021). Unfortunately, due to a number of logistical, marketing and/or regulatory obstacles, in many European countries, including Bulgaria, lack essential medicinal substances necessary for the preparation of the individualized medicinal forms prescribed. In such cases, the only approach remains the extemporaneous compounding by handling the available on the market pharmaceutical products. In addition, due to the wide age range in children and the differences that are observed during the child's physical development, the same composition cannot be applied in the whole age range, but many variations have to be developed. Another significant problem is the lack of preclinical tests and clinical trials for most medicinal products for children to ensure their safety and efficacy. This leads to increased risk of adverse drug reactions, drug interactions, side effects, including death, ineffective treatment due to inaccurate dosing, and uncertainty in physicians and parents during the therapy (Rossi et al. 2003; Rothmier et al. 2003; Tait et al. 2003; Benjamin et al. 2009; Slora et al. 2010; Beghetti et al. 2014).

Sildenafil citrate is a drug with a narrow therapeutic index. It inhibits the catalytic degradation of cyclic guanosine monophosphate (cGMP), which leads to relaxation of smooth muscle cells in the blood vessels. The drug was originally synthesized to improve myocardial blood flow and to treat angina and coronary heart disease, but in 1992 clinical trials found that its effect on cardiac blood flow was minimal but had a significant effect on blood flow in the pelvic organs, including the penis. Sildenafil citrate is used in paediatrics to treat pulmonary hypertension in neonates with single-chamber defects. Pulmonary hypertension is a disease of the pulmonary vessels characterized by a progressive increase in pulmonary vascular resistance, leading to right heart failure and death. Clinical studies have been performed to evaluate the potential use of sildenafil in infants and children (Williams et al. 2012; Wardle and Tulloh 2013). A dose of 1–5 mg/kg three times daily has been proved to be effective for paediatric patients. Although an unlicensed drug for use for children, sildenafil meets clinical requirements and is widely used in paediatric hospital wards (Tuleu and Breitkreutz 2013). As the drug is only available in tablet form, the preparation of oral liquid dosage form is suitable for both children and adults who have difficulty taking and swallowing tablets (Nahata et al. 2006; Huddleston et al. 2009; Williams et al. 2012; Roque et al. 2013; Wardle and Tulloh 2013; Provenza et al. 2014).

The aim of the present work was to propose practical applicable approaches for extemporaneous preparation of paediatric oral formulations containing sildenafil citrate for personalized therapy in children.

Materials and methods

Materials

Sucrose was purchased from Zaharni Zavodi (Gorna Oryahovitsa, Bulgaria). Fructose, crystalline was

purchased from Omnia (Adana, Turkey). Methylcellulose, 4000 CP, Nipagin, E218 and magnesium stearate were purchased from Sigma-Aldrich (Schnelldorf, Germany). Prosolv SMCC HD 90, Vivasol and Vivapur type101 were purchased from JRS Pharma (Rosenberg, Germany). Wheat starch was obtained from Roquette Pharma (Lille, France), Kollidon K25 was obtained from BASF (Hannover, Germany), talc was obtained from Brenntag (Amsterdam, Netherlands).

Preparation of vehicles

Preparation of Simple syrup (preservative free)

The simple syrup was prepared with a concentration of 64%, according to the guidelines of the European Paediatric Formulary: Simple syrup (preservative-free) monograph, 02/2023: F0008. In short, the simple syrup was prepared according to the following technological scheme: The prescribed amount of freshly boiled purified water was poured onto the sucrose, which was dissolved with continuous stirring and heating (below 100 °C to avoid caramelization) until complete dissolution. The syrup was made up to the prescribed mass with freshly boiled purified water then filtered hot through a suitable filter (in order to remove residual crystals and to homogenize).

Preparation of fructose syrup

The fructose syrup was prepared with a concentration of 55% after a literature review of fructose syrups used in Europe and worldwide (Hanover and White 1993). In short, the fructose syrup was prepared according to the following technological scheme: The prescribed amount of freshly boiled purified water was poured onto the fructose, which was dissolved with continuous stirring and heating until complete dissolution. The syrup was made up to the prescribed mass with freshly boiled purified water then filtered hot through a suitable filter.

Preparation of oral formulations containing sildenafil citrate for paediatric practice

Preparation of liquid dosage forms containing 2.5 mg/ml sildenafil citrate using API

The following procedure was applied in order to prepare oral formulations containing 2.5 mg/ml sildenafil citrate using API: three types of vehicles were used – purified water, sugar syrup and fructose syrup. The calculated amount of sildenafil citrate for 250 ml solution to be prepared was dissolved in 200 ml purified water, 200 ml sugar syrup or 200 ml fructose syrup in a volumetric flask using an ultrasonic bath for 30 minutes. 2 ml preservative solution (10% solution of methyl paraben in propylene glycol) was added to some of the samples. The solutions were then tempered and purified water, sugar syrup or fructose syrup were added to obtain a final volume of 250 ml. Afterwards they were subjected to filtration and were packaged in dark bottles for further studies.

Preparation of liquid dosage forms by processing pre-prepared model tablets

In order to prepare model tablets containing API, the amounts of active substance and excipients were weighed and sieved through a sieve with pore size of 0.5 mm and mixed in a cubic mixer at a speed of 25–30 rpm for 5 min. Depending on the excipients used, the obtained mixture was subjected to direct tableting or tableting after wet granulation using a Korch Eko (Korch AG, Germany) eccentric tablet machine with a punch diameter of 10 mm. Preparation of the working mixture used for direct tableting or tableting after wet granulation followed the classical technological scheme for this type of tableting. The technological control parameters of the tablets were established, according to the requirements of European Pharmacopoeia. The obtained model tablets were ground to a fine powder using a mortar and a pestle, for the purpose 20 tablets of each model tablet composition (Models 1–4) were used. The composition of the model tablets is presented in Table 1.

Table 1. Composition of model tablets containing sildenafil citrate.

Composition	Amount for 1 tablet (g)			
	Direct tableting		Tableting after wet granulation	
	Model 1	Model 2	Model 3	Model 4
Sildenafil citrate	0.1	0.1	0.1	0.1
Prosolv SMCC HD90	0.04	0.09	–	–
Croscarmellose sodium	0.005	0.005	–	0.005
Magnesium stearate	0.005	0.005	0.005	0.005
Wheat starch	–	–	0.235	–
Talk	–	–	0.01	0.01
Avicel PH101	–	–	–	0.220
Kollidon K25	–	–	–	0.01
Theoretical weight	0.15	0.2	0.350	0.350

The corresponding liquid carrier (sugar syrup, fructose syrup or sugar syrup and 1% aqueous solution of methylcellulose in a ratio 1:1) was added to the homogenized powder mixture containing sildenafil citrate in small portions to form a fine paste, which was then subjected to geometric dilution. The resulting suspension was transferred to a measuring cylinder and made up to 800 ml with vehicle if necessary. The suspensions were packaged in bottles for further studies.

Assessment of appearance and physical stability

The prepared model formulations were transferred in bottles (6 identical samples for each model, in order to ensure

the statistical significance of the study) and were subjected to stability study for a period of 90 days. Studies were performed at pre-selected times in order to test the parameters which could possibly change during storage period, such as appearance, pH, microbiological quality, and drug concentration.

The physical appearance properties were studied using a visual examination method of the samples stored at different temperatures (25 °C ± 2 °C and 5 °C ± 2 °C). The parameters odour, colour, or tendency to spontaneously form precipitates were appreciated. The preparations were considered stable if the physical characteristics did not change and the drug concentration remained above 95% of the original concentration.

Evaluation of the potential for redispersion of the model suspensions

This study was conducted in order to establish the minimum number of shakes, as well as the minimum angle of rotation of the bottle, in order to ensure effective redispersion of the prepared suspensions.

Determination of pH of the model compositions

The pH values were measured in triplicate using a pH meter (Mettler Toledo, Columbus, OH, USA). A significant variance of the pH for each formulation could indicate a degradation of the active substance.

Quantitative determination of sildenafil citrate in the model compositions

The amount of sildenafil citrate in the samples was determined spectrophotometrically at a wavelength of 292 nm, using a RayLeigh UV9200 spectrophotometer (Malvern Panalytical Ltd, Malvern, United Kingdom). Based on the measured absorbance, the concentration of sildenafil citrate (in μg) was calculated using pre-determined calibration curves.

Assessment of the microbiological quality

The assessment of the microbiological quality of the prepared formulations was performed at days 0 and 90 according to the European Pharmacopoeia monograph for non-sterile products (European Pharmacopoeia 11, 5.1.4 "Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use"). The microbial count was considered to be the average number of colonies forming units (CFU) found in agar. Liquid oral formulations meet microbial requirements if the total aerobic microbial count were less than 10^2 CFU/mL: maximum acceptable count = 200, the total combined yeast/mould count was less than 10^1 CFU/mL: maximum acceptable count = 20 and confirmed the absence of Escherichia coli (1 g or 1 ml).

In-use stability

The preservative-free formulations were submitted to in-use stability tests for a period of 10 days (for products containing purified water as a carrier) and 14 days (for products containing syrups as a carrier), according to the Committee for Proprietary Medicinal Product's Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP, 2001). The stability study was performed with three identical samples from each model at two different temperatures (25 °C ± 2 °C and 5 °C ± 2 °C) and relative humidity RH 60% ± 5%.

Results and discussion

Preparation of oral formulations containing sildenafil citrate for paediatric practice

Two applicable approaches for preparation of liquid formulations were applied, namely preparation using API added in a suitable liquid carrier – purified water, sugar syrup and fructose syrup, or by processing pre-prepared tablets containing API and their dispersion in a suitable carrier – sugar syrup, fructose syrup or sugar syrup and 1% aqueous solution of methylcellulose.

The use of currently available commercial products for preparation of extemporaneous formulations for children is a routine practice in hospital and community pharmacies. On the other hand, available on the market medicinal products authorized across Europe differ as strength, type, and amount of the used excipients, as the so-called generic products predominate for obvious reasons. This could cause a potential problem since it may require a different currently available on the market medicinal products to be used for preparation, which may influence the quality of the final extemporaneous preparation in terms of stability and quantitative content of the API. The generic solid dosage forms (tablets) most frequently used in extemporaneous drug forms are prepared according to well-established technologies such as direct tableting/tableting after granulation, as well as the excipients used are well known and used in widely accepted and known concentrations.

In the present study model tablets were used instead of currently available on Bulgarian market sildenafil containing medicinal products. The model tablets were formulated using well known excipients, in typical concentrations, prepared by direct tableting or tableting after granulation. The aim was to confirm the validity and applicability of the proposed preparation strategy in case when there is a need to use different, currently available on the market, generic products containing sildenafil.

The control parameters of the tablets were determined, such as uniformity of mass, disintegration, friability, mechanical strength, according to the requirements of the European Pharmacopoeia 11. The results are presented in Table 2.

Table 2. Control tests of the prepared model tablets, conducted according to the European Pharmacopoeia 11.

	Model 1	Model 2	Model 3	Model 4
Uniformity of mass	Corresponds	Corresponds	Corresponds	Corresponds
Disintegration	< 2 min	< 2 min	< 5 min	< 4 min
Mechanical strength	Sufficient	Sufficient	Sufficient	Sufficient
Friability	< 1%	< 1%	< 1%	< 1%
	0,57	0,41	0,17	0,27

Assessment of appearance and physical stability

The quality of the prepared formulations is the basis for ensuring their stability during storage and after first opening, which is closely related to their safety and efficacy. The assessment of the physical, chemical, and microbiological stability is of particular importance for liquid oral formulations.

The formulations based on sildenafil citrate with purified water as a carrier were colourless and odourless, with a slightly bitter taste, while those prepared with sugar or fructose syrup as carriers were clear to pale yellowish and sweet in taste. All tested solutions showed no change in the appearance at the storage temperatures – room temperature (25 °C ± 5 °C) and in a refrigerator (5 °C ± 2°C), throughout the whole period of stability study.

The formulations based on the model tablets were off-white to slightly yellowish suspensions with a sweet taste. The simple and fructose syrup carriers successfully masked the bitter taste of the drug substance. The precipitate formed during storage was due to the insoluble excipients used for the preparation of the model tablet compositions. The precipitation process was time-dependent related to the storage duration, i.e., the sedimentation volume decreased with increasing of the storage time. Suspensions that form deflocculated sediment were characterized by low sedimentation volume values. Suspensions with sedimentation volume values F ≥ 0.6 were considered relatively stable. The precipitate formed in the prepared formulations was redispersed relatively slowly. Fig. 1 presents the results obtained from the determination of sedimentation volume of the prepared formulations based on the model tablet compositions. Analysis of the obtained results showed that the combination of simple syrup and 1% aqueous solution of methylcellulose (1:1) provided maximum stability of the prepared compositions.

Evaluation of the potential for redispersion of the model suspensions

Ensuring uniformity of dose is extremely important for the efficiency and safety of the treatment. Therefore, study was conducted to establish the minimum number of shakes, as well as the minimum angle of rotation of the bottle, to ensure effective redispersion of the prepared suspensions. Based on the results obtained, it can be concluded that the optimal number of shakes for redispersion was

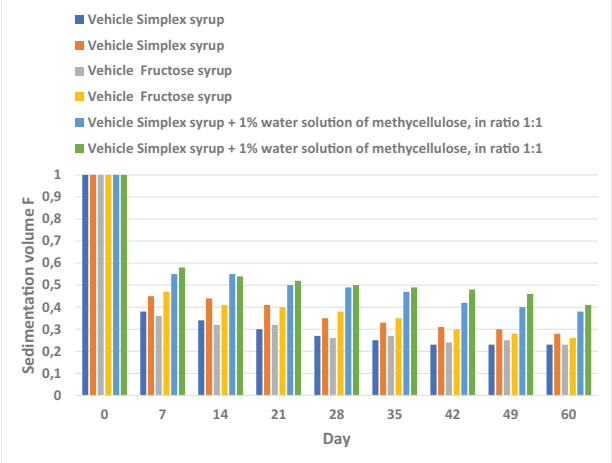

Figure 1. Sedimentation volume (F) of the suspensions at storage temperatures of 25 °C ± 2 °C and 5 °C ± 2 °C.

3 ± 1 reversible shakes, and the angle of rotation should be not less than 90° ± 15°.

pH assessment

The results obtained from the pH assessment are presented in Figs 2, 3. The pH values of sildenafil citrate oral formulations, containing or not containing a preservative, when stored in refrigerator at 5 °C ± 2 °C are presented in Fig. 2. It can be seen that the measured pH values remained relatively constant within the design of the stability study.

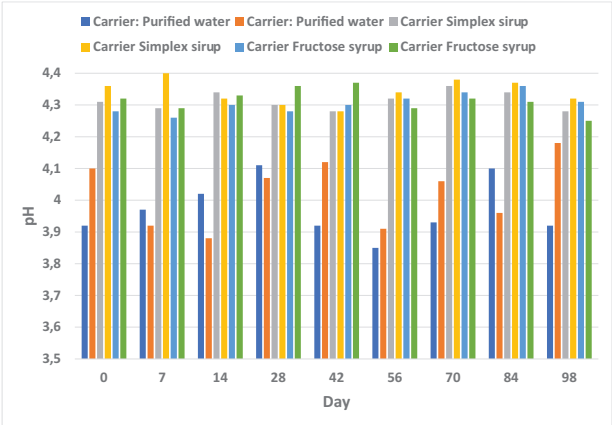

Figure 2. pH values of sildenafil citrate oral formulations, containing or not containing a preservative, after storage in refrigerator at 5 °C ± 2 °C.

When analysing the changes in pH during storage (in a refrigerator at 5°C ± 2 °C and at room temperature 25°C ± 2 °C), average pH values in the range from 3.97 ± 0.088 up to 4.34 ± 0.04 at 5 °C ± 2 °C and from 3.93 ± 0.12 up to 4.3 ± 0.06 at 25°C ± 2 °C were observed for all tested carriers. The obtained results showed that the prepared formulations remained chemically stable during the study. The pH values of the samples with simple or fructose syrup carriers were slightly higher than the formulations in which purified water was used as a carrier.

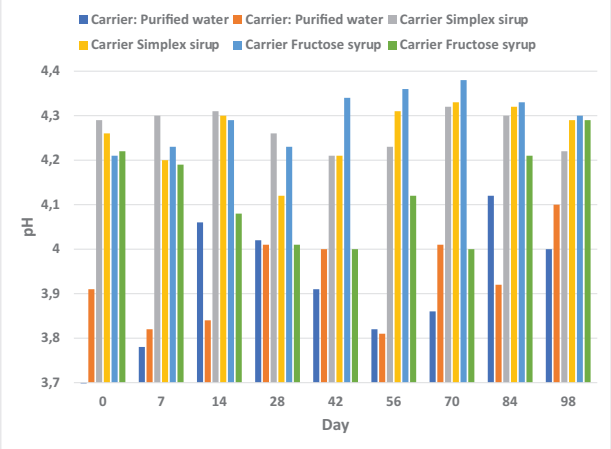

Figure 3. pH of sildenafil citrate oral formulations, containing or not containing a preservative, after storage at 25 °C ± 5 °C.

The prepared suspensions based on the model tablet formulations showed initial pH values in the range 3.9–4.4 (Figs 4, 5), while the pH values of the prepared carriers were in the range 5.2–5.5. The slightly acidic reaction of the prepared suspensions was due to the three carboxyl groups of the citrate salt. This was a potential advantage that allowed maximum solubility and permeability of sildenafil, a cationic derivative of piperazine, forming an intramolecular bond between the oxygen atom in the sulfonamide and the proton in the basic nitrogen atom in piperazine. Like the formulations prepared with the powdered active substance sildenafil citrate, the pH values remained relatively constant for 90 days, ranging from pH 3.97 ± 0.165 to pH 4.37 ± 0.12 at 5°C ± 2 °C and pH 3.9 ± 0.176 up to pH 4.36 ± 0.146 at 25°C ± 2 °C for the different formulations. Based on the obtained results, it can be concluded that the prepared formulations remained chemically stable during the experiment.

Evaluation of the content of sildenafil citrate

The results presented in Figs 6, 7 show that the content of sildenafil citrate in all oral formulations prepared with

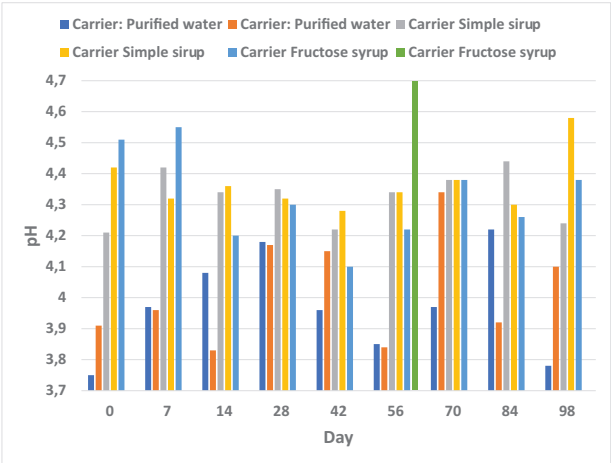

Figure 4. pH values of sildenafil citrate suspensions, containing or not containing a preservative, after storage in refrigerator at 5 °C ± 2 °C.

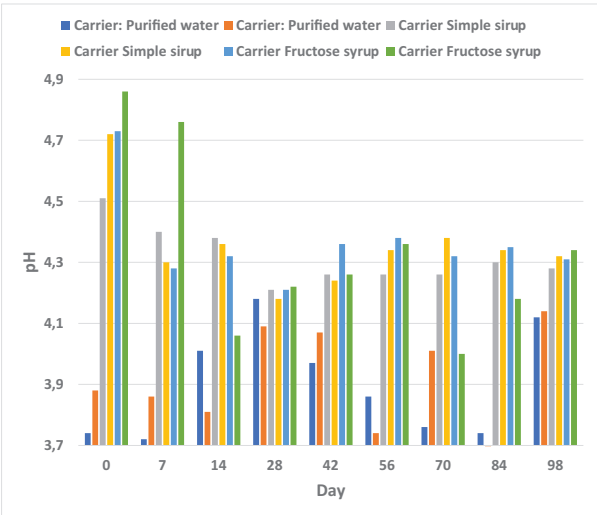

Figure 5. pH values of sildenafil citrate suspensions, containing or not containing a preservative, after storage at 25 °C ± 2 °C.

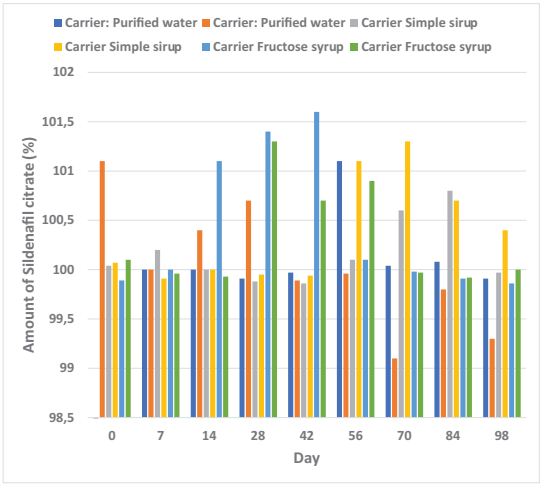

Figure 6. Content of sildenafil citrate (%) in the prepared oral formulations, containing or not containing a preservative after storage in a refrigerator at 5 ° C ± 2 ° C.

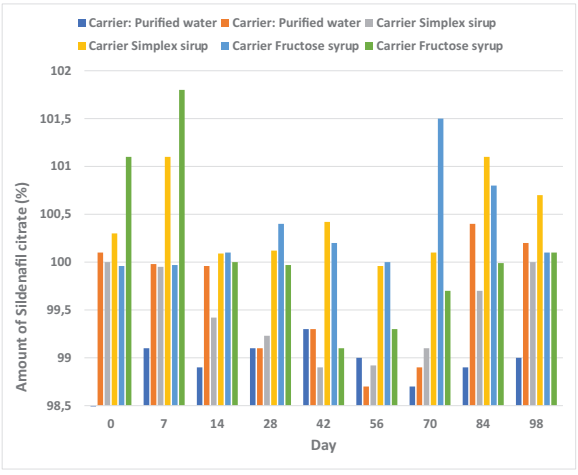

Figure 7. Content of sildenafil citrate (%) in the prepared oral formulations, containing or not containing a preservative when stored at 25 °C ± 5 °C.

API remained higher than 95% w/v, during the duration of the experiment.

When analysing changes in sildenafil citrate concentration during the storage period in refrigerator at 5 °C ± 2 °C and at room temperature 25 °C ± 2 °C, it was found that the mean concentrations ranged from 99.10 ± 0.35 to 101.8 ± 0.85 at 5 °C ± 2 °C and from 99,10 ± 0,85 to 99,96 ± 0,85 at 25 °C ± 2 °C, for all tested carriers. The obtained results showed that the prepared formulations remained stable during the experiment. The concentration of sildenafil citrate in the oral formulations with purified water, simple or fructose syrup used as carriers was higher than 95% at the end of the study.

The results from the study carried out with the suspensions prepared on the basis of model tablet formulations showed that the content of sildenafil citrate in all prepared oral formulations remained above 95% w/v, in the range 98.5 ± 0, 25% to 100.1 ± 0.15%.

Microbiological quality

The microbial contamination in non-sterile liquid formulations may cause unpleasant odour, turbidity, or could adversely affect the appearance. Furthermore, high levels of microorganisms may be dangerous to health especially in immunocompromised patients. Therefore, the assessment of the microbiological quality is of significant importance.

The microbiological quality of each formulation was assessed twice: at the beginning (Day 0) and at the end (Day 98) of the stability study. At the end of the stability study of the model formulations based on API and model tablet formulations, it was established that all samples complied with the specifications of European Pharmacopoeia 11, 5.1.4 "Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use", namely TAMC (CFU/ml) $<10^2$ and TYMC (CFU/ml) $<10^1$, as well as the absence of Escherichia coli in 1 ml/1 g. No growth of microorganisms or fungi was observed in either preservative-containing or preservative-free formulations stored at 5 °C ± 2 °C and 25 °C ± 2 °C. For both types of formulations, no Escherichia coli contamination was observed also. Therefore, it can be concluded that the use of preservatives in these formulations did not provide additional microbiological stability, but potentially might provoke severe adverse reactions, especially in early childhood.

In-use stability

Due to the fact that the formulations based on API were packaged in multi-dose containers, it was necessary to assess their stability after first opening of the container. Such tests were performed only with preservative-free solutions. Packages containing solution of sildenafil citrate in various carriers were opened twice daily in the laboratory and 1 ml was withdrawn to simulate real use. This procedure was applied for 10 consecutive days for water-based formulations and for 14 consecutive days for sugar or fructose syrup-based formulations. The obtained results are presented in Table 3. From the data presented it was obvious that the compositions retained unchanged parameters such as: appearance, pH, API content.

Conclusion

The present study revealed the potential for successful extemporaneous preparation of oral formulations with sildenafil citrate, both using pure substance (API) or using pre-prepared tablets after trituration and subsequent dispersion in a suitable liquid carrier. The main factors influencing the stability of the prepared compositions were studied and evaluated. All tested oral formulations remained unchanged in terms of appearance during the entire period of stability monitoring at the selected storage conditions – room temperature 25 °C ± 5 °C and in a refrigerator at 5 °C ± 2 °C. The established pH values suggest that the formulations remained chemically stable during the stability study. The content of sildenafil citrate in all prepared oral formulations remained higher than 95% w/v. The microbiological quality of the prepared compositions was confirmed. Stability after first opening of the package was confirmed within 10 consecutive days for water-based formulations and 14 days for sugar or fructose syrup-based formulations. The addition of preservatives in such formulations cannot be considered as an advantage, as the compositions remained stable within the shelf life, and preservatives were a potential source of severe adverse reactions, especially in early childhood age. After analysis and summarization of the obtained experimental data, the optimal conditions for the preparation of oral compositions containing sildenafil citrate were derived. A preferred approach for the extemporaneous preparation of such formulations should be preparation using API, if available. For oral suspensions, the combination of sugar solution and 1% aqueous methylcellulose solution provided maximum stability.

Limitations

The main limitations of extemporaneously prepared paediatric forms are connected with chemical, microbial, and physical stability and evaluation of bioavailability and efficacy.

Table 3. Results for the investigated parameters obtained after in-use stability study.

Formulation	Aqueous solution	Simple syrup	Fructose syrup
Appearance	Colourless, odourless, with a slightly bitter taste	Pale yellow solution, with a sweet taste	clear to pale yellow solution with a sweet taste
pH	4.03± 0.09	4.27± 0.05	4.3± 0.08
Sildenafil citrate content (%)	99.4± 0.55	99.8± 0.127	99.3± 0.145

Drugs in extemporaneously prepared liquids may be susceptible to degradation due to different chemical reactions between the API and the excipients. For example, preparations made from tablets contain various excipients such as binders and disintegrating agents that may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs.

Purified water is the main vehicle used for preparation of oral liquids and it is ideal medium for microbial growth that may cause foul odour and adversely affect the appearance or efficacy. Establishment of effective preservative systems requires thorough evaluation which is seldom performed on extemporaneous formulations because many factors can reduce the effectiveness of the preservative (Hugo and Russell 1987).

Extemporaneously prepared oral suspensions are characterized by physical instability leading to sedimentation of the insoluble drug. Difficulty in re-suspending the drug or rapid sedimentation following shaking can lead to incorrect dosing.

Bioavailability, pharmacokinetic, and pharmacodynamic studies are unlikely to be performed for most extemporaneous drugs. Also, extemporaneous formulations have not been subjected to studies establishing the efficacy and tolerability in patients (Nahata and Allen 2008).

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