ORIGINAL ARTICLE

Study of Compatibility of the Ingredients at Pharmaceutical Development of Medicine Syrup

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Abstract

Context: In the process of pharmaceutical development of syrup based on glucosamine and levocarnitine, there was a need to check the compatibility of active pharmaceutical ingredients (APIs) with auxiliary substances, which are a part of the drug in the form of syrup. **Aims:** This study aims to study the compatibility of API among themselves and with commonly used excipients settings and design: Compatibility was tested with the accelerated method by creating a mixture of APIs and auxiliary substances. **Materials and Methods:** Substances of glucosamine hydrochloride, levocarnitine, and auxiliary substances (sorbitol, xylitol, fructose, citric acid, agar, glycerin, and sorbic acid) were used. Substances' quality meets the requirements of the European Pharmacopoeia monographs and they have certificates of conformity of the European Pharmacopoeia. The quantitative determination of API in model mixtures was carried out with high-performance liquid chromatography method. Statistical analysis was used by the method of Microsoft Office Excel 2007. **Results:** Studies have shown the lack of physical-chemical interaction between API and excipients both immediately after mixing and after storage. **Conclusions:** The conducted studies did not reveal the interaction of API: Glucosamine hydrochloride and levocarnitine with each other and with selected adjuvants: Sorbitol, xylitol, fructose, citric acid, glycerol, agar, and sorbic acid, neither in dry form nor in aqueous solution. Determination of the compatibility of ingredients by the accelerated method in the created model blends is promising, convenient, and demonstrative in the development of a new medicinal product.

Key words: Glucosamine, Levocarnitine, Syrup

INTRODUCTION

Planning and conducting research on the development of a new drug must be conducted in accordance with Guideline 42–3.1: 2004 "Medicines. Guidance on quality. Pharmaceutical development," a compulsory section of the registration dossier (module 3: Quality: Chemical, pharmaceutical, and biological information about the drug containing chemical and/or biological active substances - Order of the Ministry of Health of Ukraine dated July 23, 2015, No. 460).[1] The main structural elements of the pharmaceutical development are the components of the drug, the drug, the manufacturing process, the container/packaging system, the microbiological properties, and the compatibility of the API with each other and with the excipients.[2] When choosing auxiliary matters and their concentrations, it is necessary to consider the functions and characteristics of each of them, if they can affect the functional properties of the drug (stability, bioavailability, etc.) or the possibility of its production.[3-5] Taking into account that the developed drug is intended for internal use, there is a series of medical and biological requirements such as the absence of irritating and sensitizing effects, completeness and release rate of amniotic fluid index (AFI), resistance

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to microorganisms, storage stability, and satisfactory consumer characteristics.[6] All these characteristics can be met using a variety of excipients [Table 1]. In the development of drug syrup containing levocarnitine and glucosamine hydrochloride, in quantities widely used in the treatment of the diseases of the musculoskeletal system and to increase the endurance of the body, the purpose of this study was an experimental study of the compatibility of API among themselves and with excipients.

MATERIALS AND METHODS

Substances of glucosamine hydrochloride (Calbiochem, USA), levocarnitine (Chemlaborreactiv, China), and auxiliary substances (sorbitol, xylitol, fructose, citric acid, agar, glycerin, and sorbic acid) were used. Substances' quality meets the requirements of the European Pharmacopoeia monographs and they have certificates of conformity of the European Pharmacopoeia.[5] The choice of excipient was based on the need of optimal DR composition to ensure the efficacy of AFI and the corresponding pharmacological and technological properties of the drug (accuracy of dosage, homogeneity, and viscosity), as well as the stability of the drug during the prescribed shelf life.[7]

Module 3 "Quality" requires confirmation of the absence of interaction of the API with each other and with excipient in the drug, the formation of compounds that can negatively affect the effectiveness of the drug. To confirm the lack of interaction, an organoleptic analysis of the established model mixtures and a quantitative determination of API were performed.

To study the interaction of API and excipients, interconnected models of APIs with each of the excipients were made in a 1:1 ratio, as well as in an aqueous solution. Considering that the interaction of substances is more fully manifested in solutions with higher concentration, the aqueous solutions are prepared in concentrations close to saturated, taking into account the solubility (confluency) of medicinal and auxiliary substances [Table 2].

The mixtures and solutions manufactured were stored at 75°C for 3 and 7 days. After this period, visual changes of appearance were observed and a quantitative and qualitative determination of the substances was made. The quantitative determination of AFI in model mixtures was carried out with high-performance liquid chromatography method on a liquid chromatograph "Agilent 1100."[7] Approximately 2.0 g (exact weighting) of the model mixture was placed in a 50 ml volumetric flask, 20 ml of solvent (high purity water) placed on a magnetic stirrer with heating and stirred for 20 min at 50–60°C, until a homogeneous system was obtained, which was cooled and treated with high purity water to the label. The solution was centrifuged for 10 min at 4000 rpm, and the supernatant was filtered through a nylon membrane filter with a pore size of 0.45 μm, discarding the first 2 ml of the filtrate.

Comparison solution: Approximately 10 mg of the standard levocarnitine specimen and 20 mg of the standard glucosamine hydrochloride sample were placed in a 50 ml volumetric flask, 30 ml of solvent (high purified water) stirred in an orbital shaker for 10 min until complete dissolution of the samples. The volume of the solution was provided with the same solvent to 50 ml, stirred, and filtered through a 0.45 μm pore diameter membrane filter. 5.00 ml of the resulting solution was placed in a volumetric flask of 20.0 ml and the volume of the solution was adjusted to the mark with high purity water.

The content of glucosamine hydrochloride/levocarnitine (X) in the model mixture, in percentage calculated according to the formula:

$$X = \frac{S_1\, m_0\, 550\, P\, 100}{S_0\, 50\, 20\, m_1\, 100} = \frac{S_1\, m_0\, P}{S_0\, m_1\, 4}$$

Where,

S_0 - mean value of peak area of the glucosamine hydrochloride/levocarnitine, calculated from the chromatogram of the comparison solution;

S_1 - the mean value of peak area of the glucosamine hydrochloride/levocarnitine, calculated from the chromatogram of the investigated solution;

m_0 - weight of weight gain of the standard sample of glucosamine hydrochloride/levocarnitine, in g;

m_1 - weight of sample weight, in g;

P - content of glucosamine hydrochloride/levocarnitine in a standard sample.

The efficiency of the chromatographic column, calculated for the peak of glucosamine hydrochloride and levocarnitine, was at least 5000 theoretical plates.

Experimental researches were carried out on the basis of the Department of Pharmaceutical Technology and Biopharmacy of NMAPE named after P. L. Shupyk, Department of Clinical Biochemistry, Forensic Medicine and Pharmacy KhMAPO (head - O. V. Chubenko).

RESULTS

The results of the study are shown in Table 3.

DISCUSSION

Nowadays, many dosage forms formulated are complex system containing many other components along with the API; these compounds are generally added along with

Table 1: Commonly used excipients and its role in medicinal syrups

Name	Role	Commonly used amount (%)
Sorbitol	Corrigent, stabilizer, prevents crystallization around the lid	20–35
Fructose	Flavoring, sweetener, prevents crystallization around the lid, improves the solubility of hydrophobic substances	10–60
Xylitol	Corrigent, stabilizer, moisture retainer, emulsifier	5–50 Highest single dose 5–10 g, highest daily dose 30–50 g
Agar	Prolonger, viscosity regulator, dispersant, stabilizer	1–2
Citric acid	Buffer substance for pH adjustment, antioxidant, taste corrigent	0.1–2.0
Glycerin	Correction of rheological parameters of viscous systems. At high concentration has bacteriostatic property. Used as a solvent	5–20
Sorbic acid	Preservative with antifungal and antibacterial properties. Has the highest activity at pH 4.5, the activity is significantly reduced at pH>6.0	0.1–0.2
Purified water	Solvent	Depending on the solubility of API and excipients, to the required total mass

APIs: Active pharmaceutical ingredients

Table 2: Solubility of used API and excipients in water

API and excipients	Solubility
Glucosamine hydrochloride	Very easily soluble
Levocarnitine	Easily soluble
Sorbitol	Very easily soluble
Fructose	Very easily soluble
Xylitol	Very easily soluble
Agar	High molecular matter, limitedly swelling in cold water, unlimitedly swelling in hot water with 90°C forming heat-resistant gel when cooled to 40°C
Citric acid	Very easily soluble
Glycerin	Miscible with water
Sorbic acid	Soluble in proportion 1:400

APIs: Active pharmaceutical ingredients

the APIs to protect, support, or enhance stability of the formulation.[8,9] Most of the times it is showed that the API in its pure form does not retain its stability for long which results in its denaturation, or sticking to the container wall, thus rendering it unfit, hence, to stabilize the API excipients are added which aid in maintaining the stability of the product and ensures that API retains its stability for a considerable period of time, thus improving the shelf life of dosage formulation. Data analysis [Table 3] showed the lack of physical-chemical interaction of API with each other and the auxiliary substances immediately after obtaining a model mix and during 3 and 7 days of storage at a temperature of 75°C. Therefore, API and excipients data can be used in further studies to obtain medicinal syrup. The prospect of this study is the selection of optimal auxiliary substances for the manufacture of medicinal syrup.[10,11] A check on the compatibility of APIs and excipients as well as the selection of auxiliary substances is a responsible and important part of Module 3 "Quality" of the registration dossier for the development of a new medicinal product in accordance with Guideline 42-3.1: 2004 Pharmaceutical development. The selection of auxiliary substances in accordance with their purpose and properties and the study of the interaction of API with auxiliary substances is an important stage in the pharmaceutical development of the drug.[12-15] The conducted studies did not reveal the interaction of APIs: Glucosamine hydrochloride and levocarnitine with each other and with selected adjuvants: Sorbitol, xylitol, fructose, citric acid, glycerol, agar, and sorbic acid, neither in dry form nor in aqueous solution. Determination of the compatibility of ingredients by the accelerated method in the created model blends is promising, convenient, and demonstrative in the development of a new medicinal product.

CONCLUSIONS

The conducted studies did not reveal the interaction of APIs: Glucosamine hydrochloride and levocarnitine with each other and with selected adjuvants: Sorbitol, xylitol, fructose, citric acid, glycerol, agar, and sorbic acid, neither in dry form nor in aqueous solution. Determination of the compatibility of ingredients by the accelerated method in the created model blends is promising, convenient, and

Table 3: The formulations of processed APIs, excipients, and the results of organoleptic, quantitative determination of glucosamine hydrochloride and levocarnitine.

Model mixtures components	Proportions	Changes in organoleptic properties and quantitative composition, %		
		Storage		
		0 days	3 days 75°C	7 days 75°C
Glucosamine hydrochloride	1		White powder	
		99.70±0.16	99.85±0.13	99.87±0.15
Glucosamine hydrochloride+purified water	1:1		Transparent solution	
		49.67±0.34	49.77±0.12	49.89±0.04
Levocarnitine	1		White powder	
		99.52±0.28	99.68±0.07	99.85±0.27
Levocarnitine+purified water	1:1		Transparent solution	
		49.87±0.25	49.93±0.21	49.817±0.56
Glucosamine hydrochloride+levocarnitine	1:1		White powder	
		49.87±0.39 50.00±0.14	49.9±0.10 49.9±0.20	50.067±0.47 49.733±0.05
Glucosamine hydrochloride+levocarnitine+purified water	1:1:1		Transparent solution	
		33.5±0.49 33.3±0.09	33.33±0.60 33.43±0.12	33.67±0.18 33.35±0.05
Glucosamine hydrochloride+sorbitol	1:1		White powder	
		49.97±0.25	49.87±0.59	49.87±0.61
Glucosamine hydrochloride+sorbitol (30% solution)	1:1		Transparent solution	
		49.70±0.37	49.73±0.15	49.87±0.15
Glucosamine hydrochloride+fructose	1:1		White powder	
		50.43±0.21	49.90±0.30	49.83±0.25
Glucosamine hydrochloride+fructose (40% solution)	1:1		Transparent solution	
		50.13±0.25	49.40±0.27	49.73±0.47
Glucosamine hydrochloride+citric acid	1:1		White powder	
		49.87±0.17	49.93±0.31	50.03±0.42
Glucosamine hydrochloride+citric acid (1% solution)	1:1		Transparent solution	
		49.97±0.25	50.17±0.21	49.77±0.50
Glucosamine hydrochloride+agar	1:1		White powder	
		50.13±0.125%	49.77±0,569%	50.00±0.361%

(Contd...)

Table 3: *(Continued)*

Model mixtures components	Proportions	Changes in organoleptic properties and quantitative composition, %		
		Storage		
		0 days	3 days 75°C	7 days 75°C
Glucosamine hydrochloride+agar (1% solution)	1:1	Transparent viscous solution		
		49.8±0.46	50.13±0.25	50.10±0.26
Glucosamine hydrochloride+glycerin	1:1	White suspension		
		49.77±0.25	50.13±0.15	49.73±0.12
Glucosamine hydrochloride+glycerin+purified water	1:1:1	Transparent solution		
		33.23±0.37	33.33±0.40	33.27±0.71
Glucosamine hydrochloride+sorbic acid	1:1	White powder		
		50.03±0.26	49.73±0.15	50.27±0.12
Glucosamine hydrochloride+sorbic acid (1:400 solution)	1:1	Transparent solution		
		50.23±0.094%	49.83±0.058%	50.27±0.153%
Levocarnitine+sorbitol	1:1	White powder		
		49.57±0.26	49.97±0.49	50.50±0.27
Levocarnitine+sorbitol (30% solution)	1:1	Transparent solution		
		50.10±0.14	49.97±0.12	49.87±0.38
Levocarnitine+fructose	1:1	White powder		
		49.83±0.05	50.03±0.06	49.77±0.06
Levocarnitine+fructose (40% solution)	1:1	Transparent solution		
		50.133±0.05	49.83±0.15	50.03±0.21
Levocarnitine+citric acid	1:1	White powder		
		49.90±0.16	49.87±0.31	50.17±0.06
Levocarnitine+citric acid (1% solution)	1:1	Transparent solution		
		49.90±0.16	49.78±0.20	49.87±0.06
Levocarnitine+agar	1:1	White powder		
		49.77±0.13	49.83±0,06	50.07±0.15
Levocarnitine+agar (1% solution)	1:1	Transparent viscous solution		
		50.10±0.08	50.00±0.17	49.87±0.31

(Contd...)

Table 3: *(Continued)*

Model mixtures components	Proportions	Changes in organoleptic properties and quantitative composition, %		
		Storage		
		0 days	3 days 75°C	7 days 75°C
Levocarnitine+glycerin	1:1		White suspension	
		49.50±0.29	49.80±0.10	50.13±0.21
Levocarnitine+glycerin+purified water	1:1:1		Transparent solution	
		33.27±0.05	33.43±0.28	33.47±0.05
Levocarnitine+sorbic acid	1:1		White powder	
		50.13±0.05	50.07±0.23	49.87±0.21
Levocarnitine+sorbic acid (1:400 solution)	1:1		Transparent solution	
		49.90±0.08	49.77±0.06	50.07±0.23
Glucosamine hydrochloride+levocarnitine+sorbitol	1:1:1		White powder	
		33.20±0.41	33.27±0.75	32.73±0.15
		33.23±0.05	33.27±0.12	33.47±0.06
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)	1:1:1		Transparent solution	
		33.33±0.09	33.00±0.60	33.13±0.31
		33.23±0.05	33.13±0.37	32.80±0.10
Glucosamine hydrochloride+levocarnitine+sorbitol+fructose	1:1:1:1		White powder	
		24.90±0.42	25.40±0.17	25.27±0.12
		25.03±0.25	24.93±0.15	24.87±0.45
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)+fructose (40% solution)	1:1:1:1		Transparent solution	
		24.83±0.05	25.13±0.21	25.37±0.21
		25.07±0.13	24.87±0.06	25.07±0.06
Glucosamine hydrochloride+levocarnitine+sorbitol+fructose+citric acid	1:1:1:1:1		White powder	
		20.03±0.13	20.00±0.17	19.77±0.06
		19.80±0.08	19.97±0.12	19.83±0.05
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)+fructose (40% solution)+citric acid (1% solution)	1:1:1:1:1		Transparent solution	
		20.13±0.05	19.87±0.21	19.77±0.06
		19.83±0.05	20.13±0.06	19.83±0.05
Glucosamine hydrochloride+levocarnitine+sorbitol+fructose+citric acid+agar	1:1:1:1:1:1		White powder	
		16.63±0.09	16.83±0.06	16.43±0.05
		16.53±0.08	16.70±0.10	16.70±0.10

(Contd...)

Table 3: *(Continued)*

Model mixtures components	Proportions	Changes in organoleptic properties and quantitative composition, %		
		Storage		
		0 days	3 days 75°C	7 days 75°C
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)+fructose (40% solution)+citric acid (1% solution)+agar (1% solution)	1:1:1:1:1:1		Transparent solution	
		16.73±0.05	16.77±0.06	16.67±0.05
		16.63±0.02	16.47±0.08	16.53±0.12
Glucosamine hydrochloride+levocarnitine+sorbitol+fructose+citric acid+agar+glycerin	1:1:1:1:1:1:1		White powder	
		14,23±0.05	14.27±0.05	14.27±0.15
		14.20±0.08	14.37±0.07	14.47±0.06
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)+fructose (40% solution)+citric acid (1% solution)+ agar (1% solution)+ glycerin	1:1:1:1:1:1:1		Transparent solution	
		14.27±0.09	14.37±0.07	14.33±0.01
		14.36±0.05	14.27±0.12	14.35±0.13
Glucosamine hydrochloride+levocarnitine+sorbitol+fructose+citric acid+agar+glycerin+sorbic acid	1:1:1:1:1:1:1:1	White powder		
		12.53±0.01	12.39±0.12	12.42±0.05
		12.49±0.04	12.46±0.13	12.55±0,11
Glucosamine hydrochloride+levocarnitine+sorbitol (30% solution)+fructose (40% solution)+citric acid (1% solution+agar (1% solution)+glycerin+sorbic acid (1:400 solution)	1:1:1:1:1:1:1:1		Transparent solution	
		12.48±0.06	12.41±0.09	12.55±0.01
		12.62±0.04	12.53±0.01	12.48±0.03
Glucosamine hydrochloride+xylitol	1:1		White powder	
		49.92±0.25	49.79±0.59	49.81±0.58
Glucosamine hydrochloride+xylitol (40% solution)	1:1		Transparent solution	
		49.78±0.42	49.74±0.15	49.91±0.14
Levocarnitine+xylitol	1:1		White powder	
		49.88±0.07	49.87±0.11	50.01±0.08
Levocarnitine+xylitol (40% solution)	1:1		Transparent solution	
		49.57±0.07	49.49±0.17	49.55±0.27
Glucosamine hydrochloride+levocarnitine+xylitol+sorbitol+fructose	1:1:1:1:1		White powder	
		24.69±0.51	24.71±0.19	24.70±0. 15
		25.30±0.42	25.28±0.11	25.27±0.50

(Contd...)

Table 3: *(Continued)*

Model mixtures components	Proportions	Changes in organoleptic properties and quantitative composition, %		
		Storage		
		0 days	3 days 75°C	7 days 75°C
Glucosamine hydrochloride+levocarnitine+xylitol (40% solution)+sorbitol (30% solution) +fructose (40% solution)	1:1:1:1:1		Transparent solution	
		24.97±0.17	25.02±0.21	25.01±0.21
		25.08±0.11	24.97±0.05	24.95±0.06
Glucosamine hydrochloride+levocarnitine+xylitol+sorbitol+fructose+citric acid	1:1:1:1:1:1		White powder	
		16.49±0.14	16.44±0.10	16.41±0.31
		16.52±0.08	16.49±0.14	16.45±0.17
Glucosamine hydrochloride+levocarnitine+xylitol (40% solution)+sorbitol (30% solution) +fructose (40% solution)+citric acid (1% solution)	1:1:1:1:1:1		Transparent solution	
		16.49±0.14	16.44±0.10	16,41±0.31
		16.52±0.08	16.49±0.14	16.45±0.17
Glucosamine hydrochloride+levocarnitine+xylitol+sorbitol+fructose+citric acid+agar	1:1:1:1:1:1:1		White powder	
		13.89±0.22	13.88±0.23	13.85±0.51
		14.02±0.13	13.94±0.17	13.91±0.41
Glucosamine hydrochloride+levocarnitine+xylitol (40% solution) +sorbitol (30% solution) +fructose (40% solution) +citric acid (1% solution) +agar (1% solution)	1:1:1:1:1:1:1		Transparent solution	
		13.91±0.19	13.85±0.51	13.82±0.83
		14.23±0.37	13.15±0.41	13.08±0.57
Glucosamine hydrochloride+levocarnitine+xylitol+sorbitol+fructose+citric acid+agar+glycerin	1:1:1:1:1:1:1:1		White colored suspension	
		12.51±0.17	12.49±0.83	12.47±0.15
		12.48±0.18	12.37±0.15	12.32±0.11
Glucosamine hydrochloride+levocarnitine+xylitol (40% solution) +sorbitol (30% solution) +fructose (40% solution) +citric acid (1% solution)+ agar (1% solution)+ glycerin	1:1:1:1:1:1:1:1		Transparent solution	
		12.49±0.11	12.37±0. 23	12.33±0.19
		12.51±0.15	12.49±0.50	12.47±0.37
Glucosamine hydrochloride+levocarnitine+xylitol+sorbitol+fructose+citric acid+agar+glycerin+sorbic acid	1:1:1:1:1:1:1:1:1		White suspension	
		10.89±0. 59	10.88±0.19	10.76±0.1
		10.78±0. 37	10.76±0.01	10.61±0. 37
Glucosamine hydrochloride+levocarnitine+xylitol (40% solution)+ sorbitol (30% solution) +fructose (40% solution) +citric acid (1% solution) +agar (1% solution) +glycerin+sorbic acid (1:400 solution)	1:1:1:1:1:1:1:1:1		Transparent solution	
		10.82±0.09	10.71±0.23	10.68±0.16
		10.68±0.17	10.58±0.53	10.53±0.31

APIs: Active pharmaceutical ingredients

demonstrative in the development of a new medicinal product.

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