66TH INTERNATIONAL

OPEN READINGS

CONFERENCE FOR STUDENTS OF PHYSICS AND NATURAL SCIENCES

ANNUAL ABSTRACT BOOK | 2023

Vilnius University

VILNIUS UNIVERSITY PRESS

Editors

Martynas Keršys
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Cover and Interior design
Milda Stancikaitė

Vilnius University Press
9 Saulėtekio Av., III Building, LT-10222 Vilnius
info@leidykla.vu.lt, www.leidykla.vu.lt/en/
www.knygynas.vu.lt, www.journals.vu.lt

Bibliographic information is available
on the Lithuanian Integral Library Information System (LIBIS) portal ibiblioteka.lt.

ISBN 978-609-07-0883-5 (ePDF)

DOI: https://doi.org/10.15388/IOR2023

THERMODYNAMIC CHARACTERISTICS OF THE SOLID DISPERSION SYSTEM OF DIOSMIN

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Recently, an important direction of pharmaceutical development is the search for substances effective in the treatment of disorders of the circulatory system. These substances include flavonoids, which can potentially be used to protect the cardiovascular system.

Diosmin is one of the representatives of semi-synthetic flavonoids with a wide spectrum of pharmacological properties [1]. It is used in the treatment of chronic venous insufficiency and hemorrhoidal disease, increases the vasoconstrictor effect of noradrenaline on the venous walls, increasing venous tone [2].

The main disadvantage of using diosmin as an active pharmaceutical substance is its low solubility in water, which causes low bioavailability. Therefore, to increase the degree of solubility of diosmin in water, the technique of forming solid dispersed systems (SDS) is used by the method of co-dissolving diosmin with pharmaceutically acceptable polymers and surfactants with subsequent removal of the solvent by evaporation.

The method of obtaining SDS. In a flask with a capacity of 100 ml, 45 ml of solvent were placed successively; 0.05 g of diosmin; 7.50 g of polyvinylpyrrolidone K-25 and 0.01 g of nonionic surfactant. The process of dissolving the components of the mixture was carried out by heating in a water bath (37± 0.5 °C) and intensive stirring for 30.0 ± 0.5 min. Separation of aqueous and solid phases was carried out by centrifugation at 6000 rpm. within 30.0±0.5 min. The aqueous phase (solution) was decanted and placed in a drying chamber. The drying process was carried out at a temperature of 50.0 ± 0.5 °C to a constant mass.

The solubility of diosmin in the composition of SDS was determined spectrophotometrically by the transition of the flavonoid into an aqueous solution at λ=348 nm.

According to the results of the study, the growth in the coefficient of increase in the solubility of diosmin was determined depending on the temperature. At a temperature of 25°C, this coefficient increases to 3.2 times, a slight increase is noted when the temperature rises from 25°C to 30°C (up to 3.7 times). A further increase in the temperature of the medium to 37°C allows to increase the solubility coefficient by 4.4 times, and the highest value is reached at a temperature of 40°C – 5.8 times ($p<0.05$).

Also, the stability constant (K_s) of the complexes was determined for SDS. The obtained values of the stability constant are in the range of 197.5-208.2 M^{-1}. This value indicates the favorability of the process of formation of intermolecular complexes, because it is in the optimal range (100 M^{-1} to 1000 M^{-1}).

In the reaction of complex formation, the thermodynamic interaction between the components of the system is a critical factor.

The following thermodynamic parameters were calculated for this reaction of the formation of intermolecular complexes: change in Gibbs free energy (ΔG), change in enthalpy (ΔH) and change in entropy (ΔS).

Table 1. Thermodynamic characteristics of the system

Parameters \ Temperature	25 °C (298 K)	30 °C (303 K)	37 °C (310 K)	40 °C (313 K)
ΔH^0, kJ×M^{-1}	-0,0842	-0,0842	-0,0842	-0,0842
ΔG^0, kJ×M^{-1}	-13,2195	-13,3158	-13,7449	-13,7556
ΔS^0, J×M^{-1}	44,6435±0,9322	44,2246±0,5340	44,6102±0,7583	44,2169±0,5745

The obtained data allow us to conclude that the process of formation of intermolecular complexes takes place with a slight release of energy (exothermic), since the enthalpy acquires negative values. Positive entropy values indicate that the formation of complexes between diosmin and auxiliary substances occurs when the aqueous solvate shell of molecules is destroyed. Negative values of the Gibbs free energy change indicate favorable conditions for diosmin solubilization in the presence of the polymer.

Therefore, a study of the effect of temperature on the solubility of diosmin in water as part of polymeric SDS was carried out. The obtained values show that the maximum value of increasing the solubility of diosmin is observed at a temperature of 40 °C. The thermodynamic characteristics of the system were calculated for this SDS, from which it can be seen that the process of formation of complexes is spontaneous and takes place with the release of energy.

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