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От себя лично хочу призвать всех провизоров и фармацевтов использовать Всемирный день фармацевта как прекрасную возможность для пропаганды нашей профессии, и как говорили в старину: встретим праздник достойным трудом и новыми свершениями на благо человека.

(Более подробную информацию можно найти на сайте http://www.fip.org/worldpharmacistsday)

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Новости регистрации
Обзор регистрации
лекарственных средств
Воронов Г.Г. 297

Анализ фармацевтических рынков
Маркетинговый анализ рынка
лекарственных средств для лечения
острых кишечных инфекций
Фарес Р., Бобрицкая Л.А.,
Лобова И.А., Ивко Т.И. 301

Современная аптека
Исследование проблемных
аспектов изготовления
гомеопатических лекарственных
средств в условиях аптек
Толочко В.М., Вакуленко Д.В. 309

Фармация за рубежом
Исследование зарубежного опыта
организации фармацевтического
обеспечения сельского населения
Кубарева И.В., Демяник К.О. 316

Научные исследования
Обоснование использования пробиотика,
содержащего Lactobacillus reuteri,
при экспериментальном кариесе у крыс
Трубка И.А., Савичук Н.О. 322

Разработка методики выявления
и определения активных
фармацевтических ингредиентов
в составе стоматологических пленок
Давтян Л.Л., Рева Д.В.,
Чубенко А.В., Трохимчук В.В. 328

Состояние гемопоэза у пациентов
с неходжкинскими лимфомами
Салах А.А. Абушанаб 332

Определение 2-меркаптобензотиазола
УФ-спектрофотометрическим
методом в субстанции
Антипенко Л.Н., Гладышева С.А., Васюк С.А. 339

Дифференцированная лечебная
тактика хронической обструктивной
болезни легких с учетом
клинических фенотипов
Лаптева Е.А. 347

Разработка состава и технологии
медицинских карандашей с липофильным
экстрактом коры тополя дрожащего
Альхуссейн В.В., Хохлова Л.Н. 356

Фармакоэкономика
Фармакоэкономическое обоснование
применения препарата протефлазид
в терапии папилломавирусной инфекции
Войтенко Г.Н., Коханов И.В. 361

Клиническое применение
лекарственных средств
Применение препарата Бенальгин
для купирования приступа
головной боли напряжения
в ежедневной практике врача
Наумовская Н.А., Лихачев С.А. 372

Обзоры и лекции
Систематизация структуры и синтез
магнийсодержащих лекарственных
средств и пищевых добавок
Снегирева Д.В., Снегирев В.П.,
Бевз Н.Ю., Алмакаева Л.Г. 379

Экспериментальные исследования
по выбору вспомогательных веществ
для создания лекарственного препарата
в форме твердых желатиновых капсул
Шакин Е.С., Асмолова Н.Н., Ярных Т.Г. 391

Современный подход к диагностике
и лечению взрослых пациентов
с циррозом печени с асцитом
(обзор материалов рекомендаций
Всемирной организации
гастроэнтерологов, Европейской
ассоциации по изучению
печени и Американской ассоциации
по изучению болезней печени)
Петюнин А.Г., Сипливый В.А.,
Петюнин П.А., Гринченко С.В., Доценко В.В. 398

Подготовка кадров
Обобщенный анализ средневзвешенного
показателя состава аптечных кадров
в Украине с 1913 по 1991 гг.
Пономаренко Н.С., Соловьев А.С.,
Аугунас С.В., Григорук Ю.Н. 408

Использование деловых игр при
преподавании фармацевтической химии
Кривошей О.В. 414

История медицины и фармации:
лица и события
Американское общество
истории фармации
Айрапетян Н.Р., Есьман А.О. 421

Для авторов 424

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The 2-mercaptobenzothiazole determination by UV spectrophotometric method in bulk

Определение 2-меркаптобензотиазола УФ-спектрофотометрическим методом в субстанции

Abstract

A simple, rapid, sensitive and low cost UV-spectrophotometric method has been developed for quantification of 2-mercaptobenzothiazole in bulk and validated for linearity, range, accuracy, precision, ruggedness and robustness. The valid maximum absorbance was recorded at the 324 nm in the concentration ranges 0.3–0.8 mg/100 mL of 2-MBT in water – methanol (1:1) solution after 20 min of stirring. The limit of detection was found to be 0.09 mg/100 mL, while limit of quantification was 0.26 mg/100 mL. The calibration curve was linear with r^2=0.9986. The proposed technique could be used for future studies of 2-MBT in pharmaceutical dosage forms.
Keywords: 2-mercaptobenzothiazole, validation, UV-spectrophotometry.

Резюме

Для количественного определения 2-меркаптобензотиазола в субстанции был разработан и валидирован на линейность, диапазон применения, точность, правильность, прецизионность и робастность простой, быстрый, чувствительный и недорогой УФ-спектрофотометрический метод. Максимальную оптическую плотность регистрировали при 324 нм в интервале концентраций 2-МВТ 0,30–0,80 мг/100 мл в растворе вода – метанол (1:1). Было установлено, что предел обнаружения равен 0,09 мг/100 мл, в то время как предел количественного определения – 0,26 мг/100 мл. Коэффициент корреляции составляет 0,9986. Предложенный метод может быть использован для будущих исследований 2-МВТ в лекарственных и косметологических препаратах.
Ключевые слова: 2-меркаптобензотиазол, валидация, УФ-спектрофотометрия.

■ INTRODUCTION

The antifungal resistance progressed each year against the widely used drugs, so it is always up-to-date to search for novel fungicidal agents or to investigate the old ones. 2-Mercaptobenzothiazole (2-MBT) is an important

commercial chemical, used in the production of rubber products and as a starting material to make other chemicals in USA and Europe (Fig. 1) [1]. It is also a corrosion inhibitor in oils, greases, and cooling fluids; is added as a stabilizer in polyether polymers to resist damage by air and ozone [2].

But, what is more important, it is effective antifungal agent [3, 4], also mentioned as inhibitor of dopamine β-hydroxylase [1].

Among the reported methods of 2-MBT determination were found mainly chromatographic, mass-spectrometry or electrochemical detections. Namely, application of HPLC tandem mass spectrometry in positive-electrospray ionization mode using isotope-dilution quantification [5], electrochemical [6] or UV [7] detection. Also there was GCMS method [8]. The capillary electrophoresis with amperometric detection for the simultaneous presence of 2-aminothiazole, 2-aminobenzothiazole and 2-MBT in river water [9]. The co-precipitation with Cu(II)-MBT to detect Pb^{2+} and Cd^{2+} in vegetables [10], cathodic stripping voltammetry by catalytic cobalt peak [11], or resonance Rayleigh scattering method, based on the interaction with gold nanoparticles [12]. The simplest found one was UV spectrophotometry of chloroform extract from flotation liquors, obtained after acidifying it to less, than pH 2 or after adjusting the pH to 7–8 with ammonium acetate [13].

Still, there was found no simple, fast and accurate method to determine quantity of 2-MBT in bulk in cheaper solvents, than chloroform, just by UV absorption as the most commonly used technique in the Ukrainian analytical laboratories. Hence, in this paper, such procedure of 2-MBT determination with UV-*vis* spectrophotometer is proposed and validated.

■ EXPERIMENTAL SECTION

Instrumentation

Substance was weighted using analytical balances Kern ABT 120-5DM, KERN&Sohn GmbH, Germany. UV spectra were recorded on Analytic Jena UV-*vis* spectrophotometer Specord 200 (190–400 nm), Germany.

Reagents and solutions

All of the chemicals were of the highest purity available from the LABSCAN (Ireland) and were used without any further purification. The distilled water was used throughout the experiments. Working substance of 2-MBT was purchased from "Orgsintez", Berezniki, Perm' region, Russia. CAS is 149-30-4.

According to the National Center for Biotechnology Information of U.S. National Library of Medicine data, 2-mercaptobenzothiazole synonyms also are ROTAX, AG 63, Rokon, CAPTAX, Accelm, Kaptax, Mertax, Accel M [2]. It is beige or light yellow powder with a faint odor. Molecular formula is $C_7H_5NS_2$. Formula weight is 167.25. M.p. is 177–181 °C. Density is 1.42. F.p. is 243 °C. Water solubility is <0.1 g/100 mL at 19 °C. It is stable, incompatible with strong oxidizing agents and flammable.

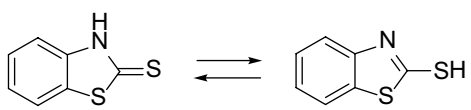

Fig. 1. 2-mercaptobenzothiazole tautomeric forms

Validation

Standard solution (0.0005% (w/V)) was prepared by dissolving 0.0500 g of the 2-MBT in the 100.0 mL flask with water – methanol (1:1) solution by thorough stirring for 20 min. Then 1.00 mL was quantitatively transferred to 100.0 mL flask and diluted in water – methanol (1:1) solution. The working standard solutions (0.0003–0.0008% (w/V)) were made quantitatively in the same way. All solutions were stored at 18–20 °C.

The analytical curve of 2-MBT was constructed by a UV-vis spectrophotometer absorption data monitored 5 times for each sample at the wavelength of maximum absorbance at the 324 nm in 3 mL cuvette with 1 cm layer.

The regression equation was obtained by the method of least squares for n=6 with regression analysis' calculations in Microsoft Excel 2007 [14]. Using this linear equation, coefficient of determination (r^2), and detection limits, linearity and accuracy were determined [15]. Precision (repeatability of the method) was evaluated by repeated absorption detection and the results were expressed as the mean standard deviation (SD) and the percent relative standard deviation RSD (%). For intra-day analysis the samples were analyzed six times a day at 09:00 am, 11:00 am, 01:00 pm, 03:00 pm, 05:00 pm, and 07:00 pm, while for inter-days stability was analyzed for 6 consecutive days at 09:00 am.

■ RESULTS AND DISCUSSION

It was already mentioned, that in 1976 year Cox proposed procedure of 2-MBT determination involving HPLC with UV detection at A max of the 325 nm in water [7] and Jones et al. in 1975 year – in chloroform extract with A max of the 329 nm [13]. So, in our studies, it was decided to use methanol-water solution (1:1), because, it's cheaper and, usually, pharmaceutical forms with as lipophilic, so hydrophilic ingredients should be diluted in it. Besides, when studying extraction of 2-MBT with chloroform, Jones et al. discussed the influence of various organic and inorganic substances presented in the flotation liquors, and had found, that only few compounds had absorption higher, than 300 nm, and even if they had, they were in so law quantity, that their absorbance lead to a very small positive error [13]. The only impurities, that could interfere, were copper cyanide or residuals of metals, that could form insoluble precipitates with 2-MBT. Still, chloroform was very expensive solvent and procedure involving acidifying the liquor to less than pH 2 or adjustion to the pH of 7–8 with ammonium acetate was too long process. Thus, water - methanol solution was considered as the most optimum choice.

The solubility of 2-MBT was lower in water (neutral pH), but in water-methanol solution, it increased, due to protonation at the pyrimidine type Nitrogen with formation of 2-MBTH^+, and (Fig. 2).

The obtained UV spectrum was in good correlation with previously obtained results by Galvão et al. [16], when they investigated the tautomeric, acid–base and ion-pair formation equilibrium of 2-MBT forms (Fig. 3).

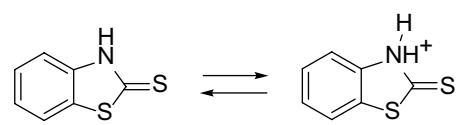

Fig. 2. 2-mercaptobenzothiazole tautomeric forms in water-methanol solution

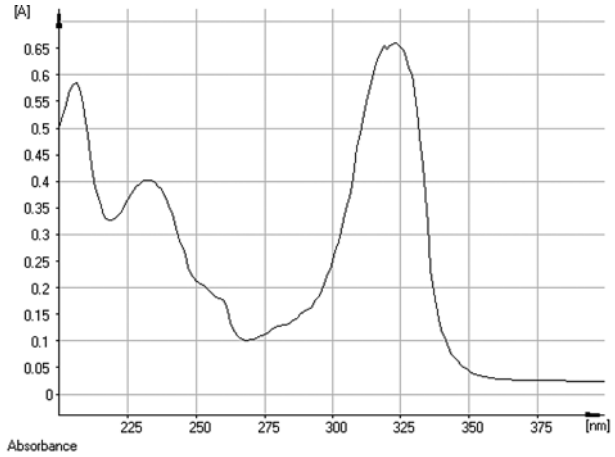

Fig. 3. UV-spectrum of 0.0005% (w/V) solution of 2-MBT in methanol-water (1:1)

The absorbance maximums were detected at the 206, the 232 and the 324 nm in methanol-water (1:1) solution. It was already experimentally and computationally proved, that the thione form of 2-MBT had more favorable hydrogen bonding and π···π stacking interactions, than thiole and equilibrium for the reaction of conversion between the associated tautomers was displaced towards 2-MBT thione isomer even in the very acidic medium (pH=2–6) [16]. In our case the pH was neutral, and in the spectrum, besides deeply discussed by Galvão et al. two thione form peaks at the 232 nm and the 324 nm, the strong peak at the 206 nm demonstrated presence of the 2-MBTH$^+$.

Consequently, the last peak at the 324 nm was chosen for investigations and, finally, the linear correlation between absorbances and concentration was achieved in range of 0.3–0.8 mg/100 mL (Fig. 4).

Validation of the method was prepared in accordance to the analytical methods validation parameters [16].

The appropriate concentrations, calculated accuracy and recovery data are presented in the table 1.

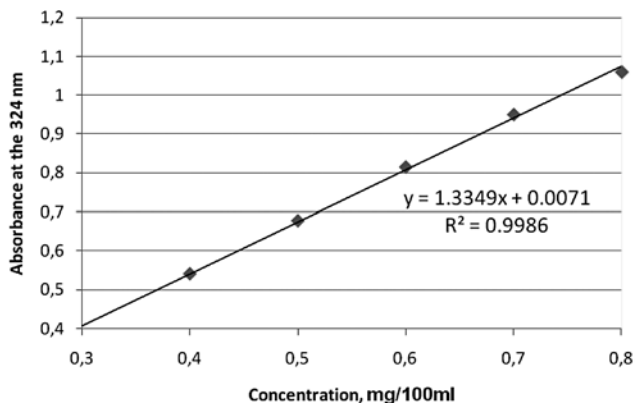

Fig. 4. Analytical curve of 2-MBT in water-methanol (1:1) solution

Table 1
Concentration of working 2-MBT solutions in water – methanol (1:1) solution, their maximum absorbances at the 324 nm, recovery and accuracy data

#	Conc., %, w/V	Conc., mg/100 mL	ΔAmax of 5 meas.	%RSD of Amax	Conc. found, mg/100 mL	Recovery
1	0.0003	0.3	0.3993	0.0417	0.2938	97.9349
2	0.0004	0.4	0.5421	0.0163	0.4008	100.1948
3	0.0005	0.5	0.6787	0.0190	0.5031	100.6218
4	0.0006	0.6	0.8157	0.0207	0.6057	100.9564
5	0.0007	0.7	0.9512	0.0181	0.7072	101.0349
6	0.0008	0.8	1.0609	0.0300	0.7894	98.6778
Mean						99.9034
SD						1.2936
RSD,%						1.1820
Accuracy, %						99.9034±1.2936
Recovery, %						99.9034±1.1820

The linearity was evaluated by linear regression analysis by the least-square regression analysis. The analytical curve of 2-MBT had good coefficient of determination – 0.9986 (Fig. 3).

The accuracy of the method was proven by recovery of six different concentrations of the calibration range (99.90±1.29%) with 99.90±1.18% percent of recoveries (table 1).

Slope, intercept and coefficient of determination were found from the regression analysis' calculations (table 2).

The limit of detection (LOD) was found to be 0.087 mg/100 mL, while limit of quantification (LOQ) was 0.264 mg/100 mL. While it was reported, that the nominal UV detection limit of chloroform extract was higher – 0.01 mg/100 mL [13], as well as for LC–MS–MS determination: LOD was 0.00004 mg/100 mL [5] and for HPLC-ED it was 0.00032 mg/100 mL [6]. Still, the paper was dealing cheap, simple method of substance detection in bulk, but not traces of the 2-MBT, according the best values of Amax – 0.6–0.8 for Beer's law. Thus, the obtained data were efficient for determination.

Calculations of the method ruggedness have shown its good reproducibility: during the day RSD was 0.61% and during the week – 1.12% (Table 3).

Table 2
Linearity data, accuracy, precision and comparison with other methods results of 2-MBT detection

Parameters	UV water – methanol (1:1)	UV chloroform [13]	LC-MS-MS [5]	HPLC-ED [6]
Slope	1.3349	–*	–	–
Intercept	0.0071	–	–	–
Linearity (mg/100 mL)	0.3-0.8	–	–	–
Regression equation	y=1.3349x-0.0071	–	–	–
r^2	0.998	0.99	0.998	0.999
SE of intercept	0.0144	–	–	–
SD of intercept	0.0353	–	–	–
LOD (mg/100 mL)	0.0873	0.01	0.00004	0.00032
LOQ (mg/100 mL)	0.2644	–	0.0001	–

* – not found in the paper.

Table 3
Intra-day and inter-day precision data of 0.0005% 2-MBT solution in water - methanol (1:1)

Amax	1	2	3	4	5	6	Mean	SD	%RSD
Intra-day	0.6787	0.6776	0.6747	0.6758	0.6698	0.6673	0.6740	0.0045	0.6069
Inter-day	0.6787	0.6756	0.6771	0.6638	0.6629	0.6604	0.6698	0.0082	1.1208

The robustness of the method was studied through temperature influence, stirring and usage of the different methanol series. It was found, that usage of the cuvette without glass cap, due to methanol evaporation, slightly resulted the absorbance results. The mechanical stirring for 20 min of each flasks and temperature of 20–25 ºC were the best conditions to obtain accurate data.

Hence, to detect the amount of 2-MBT in bulk the next methodic is proposed.

Quantitatively place 0.0300–0.0800 g of 2-MBT in the 100.0 mL flask, dissolve it in water – methanol (1:1) solution. Stir for 20 min. Quantitatively transfer 1.00 mL of obtained suspension into the 100.0 mL flask, add water – methanol solution (1:1) to obtain 0.0003–0.0008% (w/V) final solution. Stir for 10 min. Determine the amount of 2-MBT by employing UV absorption at the wavelength of the 324 nm in comparison to water – methanol (1:1) solution in 3 mL cuvette with 1 cm layer.

Calculate the sample concentration in accordance to the next calibration equation:

$$C, \% (w/V) \text{ of final solution} = \frac{Ai - 0.0071}{1.3349 \times 1000}, \quad (1)$$

where A*i* – absorbance of the investigated sample in 0.0003–0.0008% (w/V) concentration in water - methanol (1:1) solution at the 324 nm in 3 mL cuvette with 1 cm layer;

Or in comparison to measured absorption of standard solution:

$$C, \% (w/V) \text{ of final solution} = \frac{Ai \times 0.0005}{0.6787}, \quad (2)$$

where A*i* – absorbance of the investigated sample in water-methanol (1:1) solution at the 324 nm in 3 mL cuvette with 1 cm layer;

0.0005 – concentration of the standard solution with absorbance of 0.6787 at the 324 nm, % (w/V);

or concentration in the initial sample:

$$C, \% (w/V) \text{ in bulk} = \frac{Ai \times C_0 \times 100.0 \times 100.0}{A_0 \times 1.00 \times l}, \quad (3)$$

where A*i* –absorbance of the final experimental sample solution;

C_0 – concentration of the standard solution of 2-MBT is 0.0005, %;

100.0, 100.00 – flasks dilutions volume, mL;

A_0 – maximum absorbance of 0.0005% standard solution at the 324 nm is 0.6787,

1.00 – sample volume taken by pipette, mL;

l – cuvette layer, 1 cm;

■ CONCLUSIONS

It was found, that 2-MBT in bulk could be simply, low-cost, fast and accurately quantitatively determined by UV spectroscopy in water-methanol (1:1) solution by the maximum absorption at the 324 nm. Validation of the proposed method showed, that calibration curve had good linearity (R^2=0.9986) in the concentration range between 0.3–0.8 mg/100 mL. The LOD was found to be 0.09 mg/100 mL, and LOQ was 0.26 mg/100 mL. Such criteria like accuracy, precision, robustness and ruggedness also showed high validity and reproducibility, when vigorously stirring for 20 min at the 20–25 ºC. The proposed simple technique could be successfully used in developing countries in small laboratories for determination of 2-MBT in bulk or for future studies of the pharmaceutical dosage forms.

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Дифференцированная лечебная тактика хронической обструктивной болезни легких с учетом клинических фенотипов

The differentiated therapeutic tactics chronic obstructive pulmonary disease based on clinical phenotypes

Резюме

Целью исследования явилось повышение эффективности базисной терапии хронической обструктивной болезни легких (ХОБЛ). На основании выявления критериев эффективности лечения при разных фенотипах ХОБЛ установлено, что базисная терапия имеет положительное влияние на ряд параметров гомеостаза у всех пациентов, но оптимальный эффект обеспечивается дифференцированным подходом к выбору адекватного режима.
Ключевые слова: хроническая обструктивная болезнь легких (ХОБЛ), фенотипы, схемы базисной терапии.

Abstract

The aim of the study was to increase the effectiveness of chronic obstructive pulmonary disease basic therapy (COPD). Based on the identification of criteria for the effectiveness of treatment with different phenotypes of COPD, it found that basic therapy has a positive influence on a number of parameters of homeostasis in all patients, but the best effect is provided a differentiated approach to the choice of an adequate regime.
Keywords: chronic obstructive pulmonary disease (COPD), phenotypes, basic treatment scheme.

■ ВВЕДЕНИЕ

Необратимые изменения со стороны всех составляющих респираторной системы, которые неизбежно возникают в процессе прогрессирования ХОБЛ, обусловливают недостаточную эффективность лечения этой патологии. Кроме того, гетерогенность клинических проявлений и сложность патогенеза ХОБЛ требуют коррекции стандартных схем лечения и дифференцированных подходов к выбору базисных лекар-