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Research Article

Comparison of Pharmacokinetic Characteristics of Bilosomal Dispersion Versus Pure Solution of Oral Ropinirole Hydrochloride in Rats

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Abstract

Background: Ropinirole hydrochloride is a non-ergoline antiparkinson drug. It is a highly hydrophilic drug and classified as class III according to Biopharmaceutical Classification System with low absolute oral bioavailability of approximately 50% upon oral administration due to significant hepatic first-pass metabolism. **Objective:** to compare the pharmacokinetic parameters of Ropinirole when administered orally in the form of an Ropinirole bilosomal dispersion in contrast to an oral Ropinirole solution.
Methods: This study involved the use of twelve male Wistar rats, with an average weight of 220±11 g, and these rats were divided into two groups, comprising six rats each. A 1.1 mg/kg doses of pure Ropinirole and Ropinirole bilosomes were administered orally through gavage after reconstituting in distilled water. Ropinirole was quantified in the rat's plasma using HPLC, subsequently establishing a spiked calibration curve with plasma samples and utilizing paracetamol as an internal standard. The statistics included mean values (± SD; n = 6) for pharmacokinetic parameters, with statistical significance assessed using a Student's *t*-test.
Results: For the oral bilosomes, the values were 9.4±0.11 µg /ml for Cmax, 3±0.00 h for Tmax, and 55.56±2.12 µg h/ml for AUC0-24. In contrast, for the oral solution, the corresponding values were 7.2±0.14 µg/ml for Cmax, 1.5±0.00 h for Tmax, and 23.70±2.23 µg h/ml for AUC0-24. These parameters were significantly higher ($P<0.05$) as compared with a pure drug solution. The comparative bioavailability of Ropinirole (AUC0-24 oral solution / AUC0-24 oral bilosomes) is equal to 42.66%, which indicates the bioavailability of the oral RH solution was less than that of *RH* bilosomal dispersion.
Conclusions: The use of nanovesicular carriers (bilosomes) shows significant potential as an effective delivery system for improving the oral bioavailability of ropinirole hydrochloride.
Keywords: Bilosomes, Bioavailability; nanovesicular carriers; Pharmacokinetics; Ropinirole hydrochloride.

Introduction:

Parkinson's disease is the second most prevalent neurodegenerative disorder, following Alzheimer's disease. Among movement disorders, it holds the distinction of being the most prevalent (1,2).
Ropinirole hydrochloride (RH) is classified as a non-ergoline antiparkinson drug and is also utilized for treating moderate-to-severe idiopathic restless leg syndrome (3). RH has a low absolute oral bioavailability of approximately 50% upon oral administration. The limited bioavailability is primarily attributed to significant hepatic first-pass metabolism (4). Furthermore, owing to its hydrophilic characteristics (BCS class III), RH might encounter challenges in traversing biological membranes, potentially restricting its permeation within the body. The existing conventional tablet formulations of RH face challenges in achieving satisfactory oral bioavailability (5, 6). RH peak plasma concentrations are typically attained within approximately 1.5 h after oral administration. The mean elimination half-life of RH has been reported to be approximately 6 h (7).
Bilosomes are nanovesicular carriers that incorporate bile salts into their vesicle bilayer, enhancing their flexibility and resistance to degradation within the GIT. While conventional nanocarriers like liposomes and niosomes provide limited protection against enzymatic degradation in the GIT, bilosomes offer a solution to this challenge (8). The nanoscale size and inherent stability of bilosomes render them a promising candidate for oral drug delivery. Numerous studies have demonstrated their safety and efficacy in this application (9). Nonionic surfactants (NSs) are commonly employed in the formulation of bilosomes due to their notable stability and compatibility compared to other surfactants, with minimal irritation to the body's cells. They are relatively less influenced by variations in pH and ionic strength. NSs play several key roles, such as increasing permeability,

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solubilizing substances, and emulsifying liquids. They are also effective inhibitors of P-gp, which can help to improve drug absorption and increase the targeted effect of the drug on specific tissues (10,11). Bile salts incorporated into bilosomes were thought to promote the penetration of drugs and enhance oral bioavailability associated with bilosomal drug delivery might arise from the improved uptake of drugs encapsulated within bilosomes by M-cells located in the Peyer's patches, along with enhanced transport through the lymphatic pathway (8, 12).

Pharmacokinetics (PK) refers to the changes over time in the concentrations of drugs and their metabolites in the body (13). Knowledge of drugs PK is essential for obtaining safe and effective drug products (14). In addition to a conventional method for determining the PK parameter, in recent years, there has been growing interest in physiologically-based pharmacokinetic (PBPK) modeling as a new method for determining pharmacokinetics after drug delivery using the software. PBPK modeling utilizes the physicochemical properties of the drug to predict its plasma concentration-time curves. To ensure the model's accuracy, it must be confirmed against existing established clinical pharmacokinetic data (15).

The study aimed to compare the pharmacokinetic properties of ropinirole when administered orally in the form of bilosomal dispersion in comparison with oral solution.

Materials and Methods:

Materials

Ropinirole hydrochloride (Wuhan Hanweishi Pharmchem, China), Cholesterol and sodium deoxycholate (Avonchem, UK), Acetonitrile -HPLC grade (Biosolve B V, France), Ammonium acetate and Mannitol (Thomas Baker, India), Chloroform, Diethyl ether, Span®60 and Tween®60 (Loba Chemie, India).

Preparation of Ropinirole bilosomal dispersion

Ropinirole bilosomal dispersion was prepared by the reverse-phase evaporation method (16). In 10 ml chloroform and diethyl ether mixture at a 1:1 ratio, a mixture of surfactants (tween® 60 and span® 60) and cholesterol were dissolved. RH and SDC were dissolved in 2 ml of deionized water; Next, the two phases were mixed using ultrasonic baths (LiebeWh, China) to form a stable white emulsion. The solvents were removed using a rotary evaporator operating at 150 rpm and 60°C for a duration of 20 min, forming a thin film. Subsequently, the formed film was hydrated using 10 ml of deionized water in a rotary evaporator set at 150 rpm and 60°C for 60 min, and the bilosomal dispersion was sonicated for 10 minutes. Many formulas were prepared and optimized to the composition of optimized bilosomal formula and then subjected to lyophilization using a freeze dryer (Labconco, Canada) (8). The composition of the optimized bilosomal formula is shown in Table 1.

Table (1): Composition of optimized bilosomal formula of RH

Ingredient	Amount
Ropinirole Hcl	50mg
Sodium deoxycholate (SDC)	5mg
Span®60	0.9% w/v
Tween®60	1.8% w/v
Cholesterol	0.9% w/v
Deionized water	10 ml

In-vivo pharmacokinetic study

Study design: The pharmacokinetic parameters were determined using male Wister rats (n=12) with an average weight (±SD) of approximately 220 ±11 g each.

Male Wister rats were obtained from the animal house at the College of Pharmacy, University of Baghdad. These rats were allowed to acclimatize for a minimum of one week under standard conditions of room temperature (25± 3ºC). All experimental procedures were approved by the Institutional Animal Ethical Committee at the College of Pharmacy, University of Baghdad (Approval No: REACUBCPS32023A).

The rats were divided into two groups, each consisting of six rats. In Group 1, the rats were orally administered 1.1 mg/kg of pure RH solution. In Group 2, the rats were orally administered the same dose of the optimized bilosomal formula (17). Before the administration, the rats were fasted overnight but had free access to water throughout the study. The lyophilized optimized formula and pure RH powder were dissolved in distilled water based on the amount of RH in the formulation and then orally administered to the rats using a gavage tube. This method of administration ensures precise dosing of the drugs to the rats.

The blood samples were collected from the Retro-orbital venous plexus before administration of the dose to obtain a blank (zero-time point) and after administration at different time intervals at (0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24h), in EDTA vacuum glass tubes. The plasma was separated by centrifugation at 4500 rpm for 15 min and stored at −25°C until analysis (18, 19).

Analytical method

The RP-HPLC system used in this study consisted of a Sykam HPLC equipped with an S 3250 UV/Vis detector. The chromatographic separation was performed using an isocratic technique on an analytical grade C18 column with the following specifications: (150× 4.6 mm, 5 µm). A mixture of HPLC-grade acetonitrile and 0.05 M ammonium acetate buffer at pH 2.5 in a ratio of 25:75(v:v) was used as the mobile phase. Before introducing the system, the mobile phase was meticulously filtered using a 0.45µm micro-filter and degassed using bath

sonication. Throughout the analysis, the eluent was consistently monitored at a 254 nm wavelength while being pumped in isocratic mode at a steady flow rate of 1ml/min. Various dilutions of stock solutions of RH were prepared using the mobile phase. Working standard solutions of RH were prepared within a concentration range from 2.5 to 20µg/ml. An aliquot of 10µL of working standards was spiked to 100 µL of plasma separately to get concentrations of 2.5, 5, 7.5, 10, and 20µg/ml. Internal standard (IS) paracetamol (5µg/ ml) was added, followed by the above sampling procedure. 20µL of these solutions were injected for analysis. Then the standard curve was plotted by taking a concentration on X- the axis and the ratio of peak area of drug/IS on the Y-axis. Each trial was replicated three times, and the average values were reported. The sample's RH concentration was calculated from the standard calibration curve. This calibration curve determined RH plasma concentration during the *in-vivo* study (18, 20).

The validation parameters, including specificity, linearity, accuracy, precision, LLOD, and LLOQ, in rat plasma were conducted following the guidelines outlined by the US FDA for industry, specifically the guidance for bioanalytical method development and validation (21, 22).

In this study, plasma samples were subjected to processing using tert-butyl-methyl-ether as a precipitating agent for extraction. Initially, 100 µL of plasma and 100µL of IS, were mixed for 3 min. Subsequently, 500 µL of tert-butyl-methyl-ether was added to the mixture and stirred for 5 min. After that, the sample was centrifuged at 5000rpm for 15 min at 25°C, separating the supernatant organic layer. This process was repeated twice to ensure thorough extraction. The obtained organic phase was dried, and the residue was dissolved in 100µL of the mobile phase.

Additionally, control blank plasma samples (free from the drug) with and without the IS were prepared using the same procedure. Finally, the solution samples were directly injected into the HPLC column (18). Using HPLC measurements, the unknown concentration of RH could be derived based on the relative peak area. To determine primary pharmacokinetic parameters, non-compartmental analysis was implemented using PK-SOLVER. RH plasma concentrations were measured over time for both groups. Parameters such as the maximum plasma concentration of the drug (Cmax) and the corresponding time (Tmax) were ascertained. The area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24) was also calculated(19, 23,24).

Statistical analysis

All the pharmacokinetic parameter values obtained were presented as mean results of the study (± SD; n = 6). A statistically significant difference was considered when the *P*-value was less than 0.05. The pharmacokinetic parameters (Cmax, Tmax, and AUC0-24), were subjected to statistical analysis using the Student's *t*-test (25).

Results:

Calibration curve of spiked plasma samples

The calibration curve was established by implementing the recommended procedure involving the addition of a known concentration standard solution of RH to spiked plasma samples; the outcomes of HPLC analysis indicated the absence of endogenous components that could interfere with the chromatogram of blank plasma. The method demonstrated precision, specificity, and sensitivity in determining RH concentrations in standard mobile phase solutions and spiked plasma samples. The chromatogram of the spiked plasma displayed complete separation between RH and the IS, with RH exhibiting a retention time (Rt) of approximately (2 ± 0.15 min) and the IS (paracetamol) exhibiting a peak at around (6 ± 0.25 min), as depicted in figures 1 and 2.

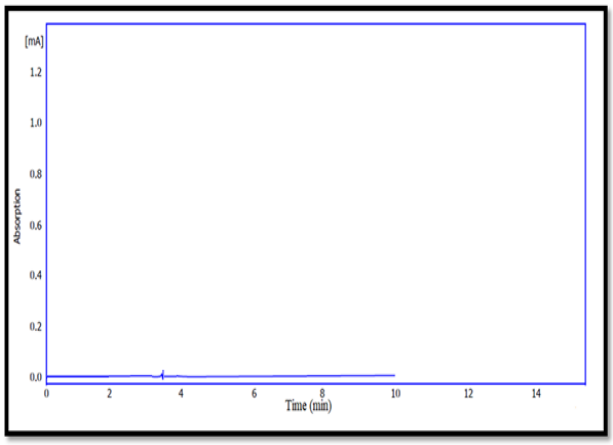

Figure (1): HPLC Chromatograms of blank rat plasma.

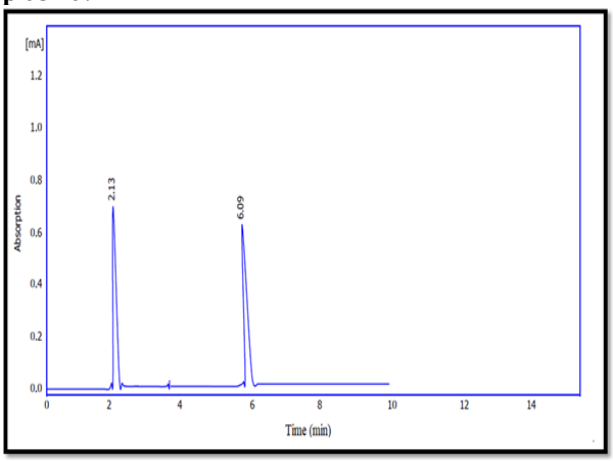

Figure (2): HPLC Chromatograms of RH in plasma spiked with IS.

Figure 3 displays the calibration curves of RH, obtained by plotting the ratio of the peak area of the drug/IS against the drug concentration. These curves exhibit a straight line and a high correlation

coefficient of 1, indicating that they follow a linear relationship within the concentration range used in the experiment. (18,20).

The precision and accuracy of the method were assessed by analyzing replicates of samples covering the linearity range at three concentrations on three different days. The coefficients of variation (CV) for intra-day and inter-day precision were 0.96-1.57 % and 1.21- 1.47%, respectively, with a low % CV (<2%), indicating high precision. The intra-day and inter-day accuracies for RH were 95.40-104.0% and 95.20- 103.4% respectively. The results presented in table 2, demonstrated that the method was both accurate and precise (26,27). In this study, the LLOD was determined to be 0.024 µg/mL, while the LLOQ was found to be 0.075 µg/mL, with a standard error of the intercept (2.514) and a standard deviation of the intercept (6.636). All validation parameters were within acceptable criteria (22).

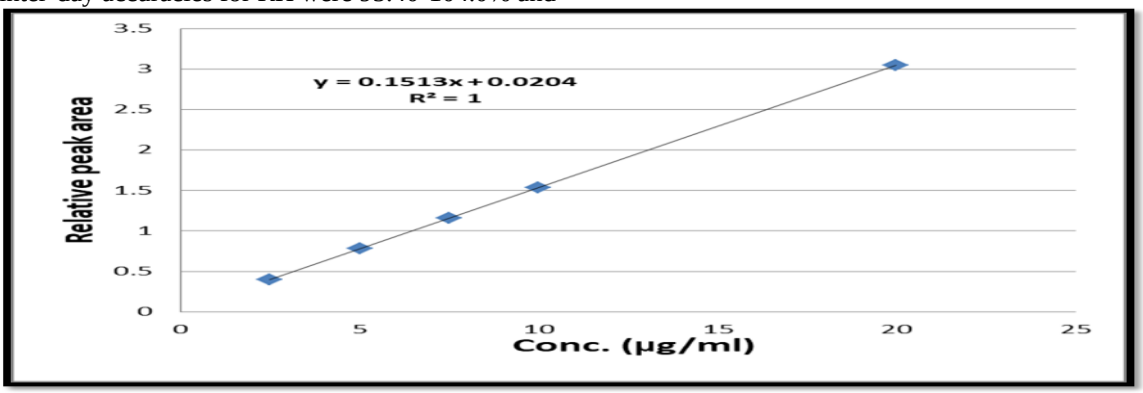

Figure (3): Calibration curve for the estimation of RH in rat plasma.

Table (2): Precision and Accuracy of the HPLC Method in Rat Plasma for RH

RH concentration (µg/ml)			CV %		Accuracy %	
	Intra-day*	Inter-day*	Intra-day	Inter-day	Intra-day	Inter-day
5	4.77	4.76	1.22	1.21	95.40	95.20
7.5	7.34	7.40	1.57	1.35	97.86	98.70
10	10.40	10.34	0.96	1.47	104.0	103.4

*Results expressed as mean ± SD, n=3

Ropinirole bilosomes pharmacokinetics: The pharmacokinetic evaluation of the optimized bilosomal formula was conducted after oral administration and compared with the oral solutions of the pure drug. Throughout the study, the test products were well tolerated by the rats, as there were no observed adverse effects or allergic reactions. Figure 4 shows the RH oral solution's plasma concentration versus time profiles and optimized bilosomal formula. Additionally, the pharmacokinetic parameters of the oral solution of RH and optimized bilosomes formula were presented in Table 3.

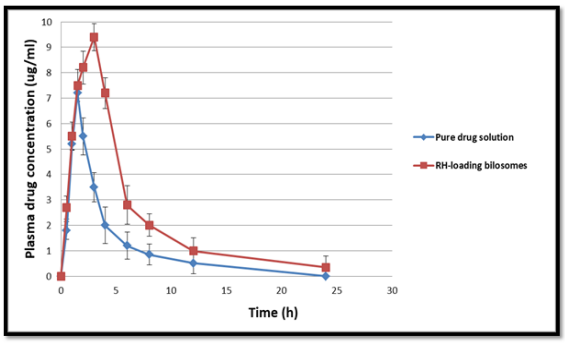

Figure (4): Plasma Concentration (µg/ml) of optimized bilosomal formula and Pure RH solution vs. time (h).

Table (3): Pharmacokinetic parameters of Optimized Bilosomal Formula and Pure RH Solution

Parameter	Unit	Pure RH solution	Optimized bilosomal formula
Cmax	µg/ml	7.2±0.35	9.4±0.24
Tmax	h	1.5±0.00	3±0.00
AUC 0-24	µg. h/ml	23.70±1.02	55.56±2.97

Results expressed as mean ± SD, n=6

The pharmacokinetic parameters of Ropinirole Hydrochloride (RH) were evaluated for both oral solution and oral optimized bilosomal formula. The maximum plasma concentration (Cmax) of RH was determined to be (7.2±0.14 µg/ml) for the oral solution and (9.41±0.11 µg/ml) for oral bilosomes, indicating an approximately 1.3-fold increase in Cmax for the optimized bilosomal formula compared to the RH oral solution.

Additionally, the area under the concentration-time curve from 0 to 24 hours (AUC0-24) value of the optimized bilosomal formula was significantly higher ($p < 0.05$) compared to the AUC0-24 value of the RH oral solution.

The AUC 0-24 value of RH bilosomes was (55.56±2.12 µg h/ml), while those of the RH solution was (23.70±2.23 µg h/ml). The comparative bioavailability of RH (AUC0-24 oral solution / AUC0-24 oral bilosomes) was equal to 42.66%.

Discussion:

The results demonstrate the successful establishment of a calibration curve for RH quantification using HPLC in plasma samples. Notably, the analytical method showed precision, specificity, and sensitivity in measuring RH concentrations in both standard mobile phase solutions and spiked plasma samples. These findings indicated a reliable and accurate analytical method for RH analysis in plasma.

The significantly higher Cmax of the optimized bilosomal formula suggests an improved drug delivery profile via bilosomes, overcoming the limitations of poor delivery observed in the oral solution. Moreover, the prolonged release of RH from the vesicles in the bilosomes contributes to a more prominent time to reach maximum concentration (Tmax) for the optimized bilosomal formula compared to the oral RH solution (28,29).

The study shows that the bioavailability of oral RH solution was less than the RH bilosomal dispersion. However, This indicates an enhancement in the bioavailability of optimized bilosomal formula compared to the RH oral solution, attributed to enhanced permeation across the GIT (29- 32).

The higher Cmax and AUC 0-24 values observed for RH bilosomes can be attributed to various factors, including improved drug retention due to enhanced entrapment within the bilosome vesicles, sustained release properties, smaller vesicle size facilitating GIT absorption, and avoid of first-pass metabolism. These factors collectively contribute to the promising pharmacokinetic profile of optimized bilosomal formula (33, 34).

The enhanced uptake of intact RH bilosomal vesicles by the M cells in the Peyer's patch of the intestinal part in the GIT and their absorption via carrier-mediated transport are believed to be crucial factors contributing to the significantly higher comparative bioavailability compared to RH solution ($P < 0.05$) (28,35).

This study suggests that the optimized bilosomal formulation offers an alternative to the traditional dosage form of RH, with promising pharmacokinetic characteristics. The absence of adverse effects of optimized bilosomal formulation in rats and the pharmacokinetic data support the potential benefits of the bilosomal formulation for drug delivery and therapeutic effectiveness.

Conclusions:

The pharmacokinetic parameters (Cmax, Tmax and AUC0-24) of bilosomal dispersion of oral ropinirole hydrochloride were better than those of its pure oral solution which might indicate that bilosomal preparations can enhance bioavailabilty of orally-administered highly hydrophilic drugs.

Limitation: The study has no any limitation

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Authors' Declaration:

We confirm that all the figures and tables in the manuscript are mine/ ours. Authors sign on ethical consideration's approval-Ethical Clearance: The project was approved by the college's in-animal Ethical committee of Pharmacy, University of Baghdad. According to the code number (Approval No: REACUBCPS32023A).

Conflicts of Interest: None.

Authors Contributions:

Study conception & design: Entidhar J. Al-Akkam1). Literature search: (Entidhar J. Al-Akkam1& Samer K. Ali). Data acquisition: (Samer K. Ali). Data analysis & interpretation: (Samer K. Ali). Manuscript preparation: (Entidhar J. Al-Akkam1& Samer K. Ali). Manuscript editing & review: (Entidhar J. Al-Akkam1& Samer K. Ali).

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مقارنة الخصائص الحرائك الدوائية لمنتشر بيليوسومال مقابل المحلول النقي لروبينيرول هيدروكلوريد عن طريق الفم في الجرذان

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خلفية البحث : روبينيرول هيدروكلوريد هو دواء مضاد للباركنسون غير إرجولين. وهو دواء محب للماء للغاية ويصنف ضمن الفئة الثالثة وفقًا لنظام تصنيف الأدوية الحيوية مع توافر حيوي عن طريق الفم منخفض بنسبة 50٪ تقريبًا عند تناوله عن طريق الفم بسبب استقلاب الكبد الأول.
الاهداف: مقارنة الخصائص الحركية الدوائية الصيدلانية للروبينيرول عند إعطائه عن طريق الفم في شكل منتشر بيليوسومال للروبينيرول مقابل محلول فمي للروبينيرول.
طرق العمل : شملت هذه الدراسة استخدام اثني عشر جرذ ويستار ،بمتوسط وزن كل منها حوالي 220 ± 11 جم ، وتم تقسيم هذه الجرذان إلى مجموعتين ، تضم كل مجموعة ستة جرذان. تم إعطاء جرعة
1.1 مجم / كجم من وزن الفارعن محلول الدواء النقي والروبينيرول بشكل بليبليوسومات عن طريق الفم من خلال الانبوب بعد إعادة تكوينها في ماء مقطر. بعد إعداد منحنى المعايرة باستخدامHPLC تم قياس كمية الدواء في عينات البلازما وذلك باستخدام مركب الباراسيتامول كمعيار داخلي. وتضمنت الإحصائيات القيم المتوسطةSD ±) ؛ (n = 6 لمعلمات الحرائك الدوائية، مع تقييم الدلالة الإحصائية باستخدام اختبار الطالب
Cmax , Tmax, AUC0-24
النتائج: بالنسبة للبيليوسومات الفموية، كانت القيم 9.4 ± 0.11 ميكروغرام / مل لـCmax ، و3 ± 0.00 ساعة لـTmax ، و55.56 ± 2.12 ميكروغرام / مل لـ .AUC0-24 في المقابل، بالنسبة للمحلول الفموي، كانت القيم المقابلة 7.2 ± 0.14 ميكروغرام / مل لـCmax ، و1.5 ± 0.00 ساعة لـTmax ، و23.70 ± 2.23 ميكروغرام / مل لـ .AUC0-24 كانت هذه المعلمات أعلى بكثير (P <0.05) مقارنة بالمحلول الدوائي النقي. التوافر الحيوي المقارن لروبينيرول (AUC0-24 محلول فموي AUC0-24 / بيلوسومات فموية) يساوي 42.66%، مما يشير إلى أن التوافر الحيوي لمحلول RH الفموي كان أقل من منتشر البيليوسومال لـRH .
الاستنتاجات: ان استخدام الناقلات الحويصلات النانوية البيليوسومات تظهر امكانيات كبيرة كنظام توصيل فعال لتحسين التوافر الحيوي لدواء روبينيرول هيدروكلوريد.
الكلمات المفتاحية : البيليوسومات , التوافر الحيوي , الناقلات الحويصلية النانوية, الحرائك الدوائية , روبينيرول هيدروكلوريد .