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DISSOLUTION CHARACTERISTICS OF NICARDIPINE HYDROCHLORIDE MICROCAPSULES FROM HARD GELATIN CAPSULES AND TABLETS*

NİKARDİPİN HİDROKLORÜR MİKROKAPSÜLLERİNİN SERT JELATİN KAPSÜL VE TABLETLERİNİN DİSSOLÜSYON ÖZELLİKLERİ

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Nicardipine hydrochloride microcapsules prepared by using ethylcellulose as coating material were put into hard gelatin capsules and were comparessed into tablets to investigate the effect of direct tableting agent on the release of nicardipine hydrochloride. Dissolution tests were studied in simulated gastric medium without enzyme using the USP XXII rotating basket method. In vitro release was evaluated by zero order, first order, RRSBW, Hixson-Crowell, Higuchi and Hopfenberg kinetic models. The release of nicardipine hydrochloride was found to be governed by the core: wall ratio, microcapsule particle size and the kind of direct tabletting agent. Release from hard gelatin capsules and tabletted microcapsules were significantly more prolonged than the respective batches of the microcapsules, but release of tabletted microcapsules was found to be low degree for drug. Therefore, direct tabletting agents such as lactose, lactose fast flo and avicel pH 101 were added to the tablets to increase the release rate of drug. It was concluded that avicel pH 101 could be used to increase dissolution rates from tabletted microcapsules.

The multiple regression technique was assumed for the analysis of experimental data. Three-dimensional response-surface graphs for percentage of nicardipine hydrochloride released as a function of percentage of drug content and dissolution time were generated.

Kaplama materyali olarak etilselüloz kullanılarak hazırlanan nikardipin hidroklorür mikrokapsüllerinden nikardipin hidroklorürün serbestleşmesi üzerine dağıtıcıların etkisini incelemek için, sert jelatin kapsüllere doldurıldu ve tablet halinde basıldı. Dissolüsyon testleri, USP XXII döner sepet metodu kullanılarak enzimsiz suni mide vasatında yapıldı. In vitro salım, sıfırıncı derece, birinci derece, RRSBW, Hixson-Crowell, Higuchi ve Hopfenberg kinetik modelleri ile değerlendirildi. Nikardipin hidroklorür serbestleşmesinin dağıtıcının cinsi, mikrokapsül partikül büyüklüğü ve çekirdek:çeper oranına bağlı olduğu bulundu. Sert jelatin kapsül ve tabletlerden ilaç serbestleşmesi, mikrokapsüllere nazaran daha uzatılmış etkidedir, fakat tabletlerde ilaç serbestleşmesi düşük bulunmuştur. Bundan dolayı serbestleşen ilaç miktarını artırmak için, tabletlere laktoz, laktoz fast flo ve avicel pH 101 gibi dağıtıcılar ilave edildi. Bu çalışmada, mikrokapsüllerden hazırlanan tabletlerden çözünürlüğün arttırılması için avicel pH 101'in kullanılması sonucuna varılmıştır.

Deneysel verilerin değerlendirilmesi için, çoklu regresyon tekniği düşünülmüştür. Nikardipin hidroklorürün yüzde salımının, yüzde ilaç miktarı ve dissolüsyon zamanının bir fonksiyonu olarak üç boyutlu yüzey cevap grafikleri tasarlandı.

Keywords : *Nicardipine hydrochloride microcapsules; core:wall ratio; microcapsule particle size; direct tabletting agent; dissolution test; response-surface graphs*

Anahtar kelimeler: *Nikardipin hidroklorür mikrokapsülleri; çekirdek:çeper oranı; mikrokapsül partikül büyüklüğü; dağıtıcı ajan; çözünme hızı testi; yüzey-cevap grafikleri*

Introduction

Nicardipine hydrochloride (Nd.HCl) is a new calcium channel-blocking agent, classified with the dihydrochloride derivatives (1,2). Various formulations have been proposed for the administration of Nd.HCl. Tablets, hard gelatin capsules and coated pellets have been suggested for oral release formulations (3,4). Recemtly, this drug was widely used for the treatment of hypertension, angina pectoris and cerebrovascular diseases but its bioavailability is very limited (15-45%) (5,6). Its elimination half-life is very short (about 1 hour) and it has some side effects such as nausea, vomiting, flushing, headache, dyspepsia, anorexia, diarrhea, probably due to rapid absorption or gastric irritation (3,7). Therefore, various sustained release formulations such as alginate beads, tablets, granules and microcapsules of Nd.HCl have been presented (8-11). In a study,

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physicochemical properties of Nd.HCl and its microcapsules have been investigated (12). Various studies concerning sustained release microcapsules formulated into tablets and capsules have been reported (13-17). A number of studies covering the effects of direct tabletting agents (DTA) such as lactose, avicel pH 101 and primojel on the tablets prepared from phenylpropanolamine hydrochloride, dihydralazine sulfate and acetaminophen microcapsules have been reported (14,17,18).

The purpose of this investigation is to study in vitro release kinetics of ethylcellulose coated Nd.HCl microcapsules formulated into tablets and capsules. In addition, the prepared microcapsules were compressed by using differents types of DTA such as lactose, lactose fast flo and avicel pH 101.

The main objective of our study was to prepare sustained action Nd.HCl microcapsules formulated into tablets and capules in order to overcome the development of tolerance seen in conventional preparations, and to increase patient compliance. In addition, in this study it was aimed to investigated the effects of DTA on the release rate of drug.

Materials and Methods

Materials

Nicardipine hydrochloride (Yamanouchi Pharm. Co. Ltd., Japan); ethylcellulose (ethoxy number 48 and Type N-10) (Sigma, St. Louis, USA); cyclohexane (E. Merck, Darmstadt, Germany); avicel pH 101 (Marcus Hook, Pennsylvania, USA); lactose (E. Merck, Darmstadt, Germany); lactose fast flo (Seppic, Paris, France); the other chemicals used were of analytical grade.

Methods

Preparation of nicardipine hydrochloride microcapsules

The method of preparation was developed by modifying the techniques of Jalsenjak et al. (1976), Salib et al. (1976) and Sevgi et al. (1994) (19-21). The preparation of microcapsules was given elsewhere (10). Quantities of Nd.HCl and ethylcellulose used depending on the core:wall ratio are shown in Table 1.

Assay of nicardipine hydrochloride

Batches of 10 mg powdered microcapsules of different core:wall ratio were extracted 10 times with 10 ml simulated gastric fluid (SGF) without enzyme (22). Nd.HCl was assayed spectrophotometrically at 239 nm.

Particle size distribution

Particle size distribution of the microcapsules was determined by sieving. Hard gelatin capsules and tablets were prepared from microcapsules retained at sieves of 840-247 μm sizes and were used in the dissolution experiments.

Table 1. Amounts of nicardipine hydrochloride and ethylcellulose used for different core:wall ratios of microcapsules

Core:wall ratio	Nicardipine hydrochloride (g)	Ethylcellulose (g)
2:1	8	4
1:1	4	4
1:2	2	4

Content uniformity and microcapsule recovery

The microcapsules were weighed after being dried. Since the amount in grams of the added material was known, microcapsule recovery was determined.

Preparation of hard gelatin capsules

Nd.HCl microcapsules of different core:wall ratios and of different microcapsule sizes were filled into hard gelatin capsules (Table 2). The amount of microcapsule fed into the die corresponds to 20 mg Nd.HCl.

Table 2. Codes of Nd.HCl microcapsules formulated into hard gelatin capsules and tableted microcapsules

Core:wall ratio	Particle size (μm)	Code	
		Hard gelatin capsules (Capsule No)	Tableted microcapsules
2:1	>840	C1(0)	T1
	840-476	C2(0)	T2
1:1	>840	C3(00)	T3
	840-476	C4(0)	T4
1:2	>840	C5(00)	T5
	840-476	C6(00)	T6
Conventional tablet		L	
Pure drug		N	

Preparation of tablets

Tablets were prepared from Nd.HCl microcapsules of different microcapsule sizes as coded in Table 2. Tablets of 2 kg hardness were compressed by hand using a single-punch tableting machine. The amount of microcapsule fed into the die corresponded to 20 mg Nd.HCl. These microcapules were tabletted with different types of DTA. Lactose, lactose fast flo and avicel pH 101 were added as DTA. The amounts of lactose, lactose fast flo and avicel pH 101 were determined as 10 per cent of the microcapsule weight according to the results of preliminary experiments. Coded numbers of tabletted microcapsules prepared with lactose, lactose fast flo and avicel pH 101 are shown in Table 3.

In addition, dissolution experiments were repeated using 25, 50% DTA to investigate kind and amount effect. According to kinetic evaluations highest determination coefficient results were obtained with 2:1 core:wall ratio microcapsules which have 840-476

Table 3. Codes of nicardipine hydrochloride microcapsules formulated into tabletted microcapsules with 10% direct tabletting agent.

Core:wall ratio	Particle size (μm)	Direct Tabletting Agent (DTA)		
		Lactose	Lactose fast flo	Avicel pH 101
2:1	>840	T1A	T1B	T1C
	840-476	T2A	T2B	T2C
1:1	>840	T3A	T3B	T3C
	840-476	T4A	T4B	T4C
1:2	>840	T5A	T5B	T5C
	840-476	T6A	T6B	T6C

Table 4. Codes of nicardipine hydrochloride microcapsules formulated into tabletted microcapsules with 25 and 50% direct tabletting agent.

Core:wall ratio	Particle size (μm)	Direct Tabletting Agent (per cent)		
		Lactose	Lactose fast flo	Avicel pH 101
2:1	840-476	25 T7A 50 T8A	25 T7B 50 T8B	25 T7C 50 T8C

μm particle size. These microcapsules code numbers are shown in Table 4.

In vitro dissolution rate experiment

Dissolution from microcapsules were studied using the USP XXII rotating basket method(22). 900 ml of simulated gastric fluid (SGF) without enzyme were placed in the dissolution apparatus. The mesh size of the basket was 40. The water bath was maintained at 37.5±0.1°C and constant speed motor was calibrated to provide 100 rpm stirring rate throughout the test. Samples of 2 ml were removed at time intervals and 2 ml dissolution medium was added to the system. The Nd.HCl contents of hard gelatin capsules and tabletted microcapsules which contained DTA were determined spectrophotometrically at 239 nm. Commercially available tablets and pure drug were tested. All samples were run in triplicates and the means were calculated.

Kinetic evaluation of dissolution rate results

The data obtained from Nd.HCl microcapsules formulated into tablets and capsules were evaluated kinetically by zero order, first order, RRSBW, Higuchi, Hopfenberg equations (23-29). The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer program (30). The results of dissolution studies obtained were compared and evaluated kinetically and the most convenient model for the release of Nd.HCl was determined. *Mathematical evaluations*

In order to explain the variation in % release of Nd.HCl from capsules and tablets, a multiple linear regression model has been assumed. This model was in the form of :

$$y=\alpha+\beta_1 x+\beta_2 \log t+e \qquad \text{(Eq.1)}$$

where, y is the observed % release of drug, e is the eror term. α, β_1 and β_2 are the coefficients to be estimated. x and logt are % drug content and logarithm of time, respetively.

SPSS statistical analysis package has been used for statistical evaluations of the experimental data (31).

Results and Discussion

In this investigation ethylcellulose with a viscosity of 10cp was chosen as the wall material and the coacervation phase separation method was employed. Ethylcellulose was selected as the wall material for its widely usage in suspension formulations and as wall material in tablets and has no side effects (32,33).

Particle sizes of the microcapsules were determined by sieve analysis. Since particle size is one of the important factors in affecting the release profiles of microcapsules (17-19), three different particle sizes: 476-247 μm; 840-476 μm; >840 μm were separated and 840-476 μm; >840 μm used for the release rate experiments. 476-247 μm microcapsules were not used, because of their low recovery.

Since the amount of the active substance in the particles changes depending on particle size and core:wall ratio, recovery was measured in all the microcapsule formulations prepared (Table 5) and it was low in microcapsules with core:wall ratio 1:2 compared to 1:1 and

2:1. As the amount of ethylcellulose was increased, the amount that adheres to the glassware and to the filter paper increased, thus the recovery reduced.

Table 5. Recovery of microcapsules prepared using 10cp ethylcellulose

Core:wall ratio	Total summation	Particle size (μ) >840	840-476	476-247
	% Recovery			
2:1	94.41	39.27	58.95	1.76
1:1	95.87	17.99	75.62	6.38
1:2	77.50	20	74.83	5.16

The calibration equation of y=0.0506x+0.036 (r=0.99) was used for the determination of the Nd.HCl (y=absorbance; x=concentration μg/ml). The sensitivity was found within the range of 2.5-15 μg/ml. Analysis of variance which belongs to the correlation between x and y is given in Table 6. As a result lack of fit test is found to be insignificant.

Table 6. Analysis of variance

SOURCE	DF	SS	MS	F
Regression	1	0.84005	0.84005	2896.72
Error	16	0.00467	0.00029	
Total	17	0.84473		

p<0.01 %CV=%3.77

The most frequently used dosage forms for microencapsulated products have been suspension, gel and hard gelatin capsule. Only a few investigations of tablet formulations from microcapsules have been reported by using DTA (16-18,34). Therefore the purpose of this investigation was to compress the respective batches of microcapsules into their tablets and study the release kinetics of the drug from them.

Dissolution results obtained from gelatin capsules are shown in Fig.1. The in vitro drug release was sustained from 30 minutes to 5 hours. Tabletted microcapsules were prepared in order to obtain a better sustained action than hard gelatin capsules. Dissolution results of tablets prepared from microcapsules are shown in Fig.2. Although drug release was sustained to 8-9 hours, the amount of drug release was

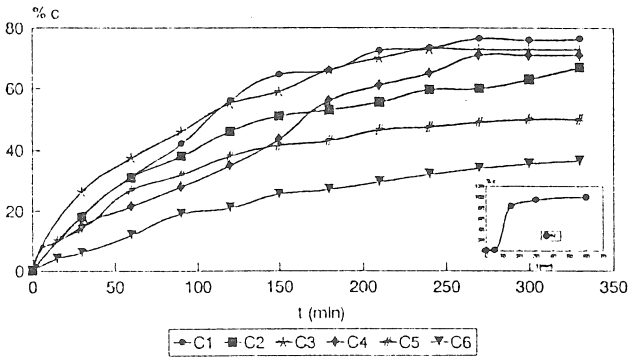

Fig.1. Dissolution profiles of pure drug (N) and nicardipine hydrochloride microcapsules formulated into hard gelatin capsules

found very low (20-46%). Therefore; in order to increase the drug release, 10% of DTA such as lactose, lactose fast flo and avicel pH 101 were added to the tablets. These disintegrants were chosen because of their easily dispersability and freely solubulity in water.

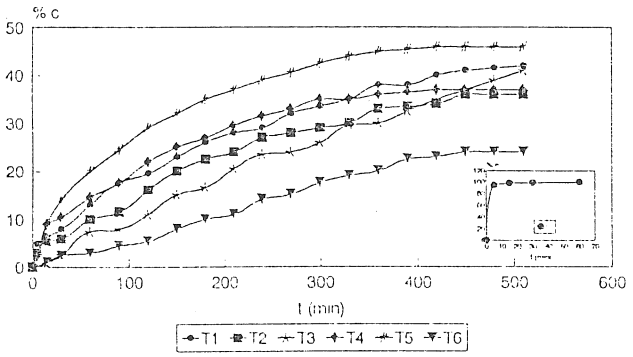

Fig.2. Dissolution profiles of commercial tablet (L) and nicardipine hydrochloride tabletted microcapsules

In a previous study, 50% lactose, primojel and avicel pH 101 have been added as DTA to phenylpropanolamine hydrochloride tablets prepared from microcapsules. Also in this study it has been shown that lactose prolonged the release of phenylpropanolamine hydrochloride more than avicel pH 101, whereas, primojel released the active principle more rapidly than avicel pH 101 (17). In a similar study dihydralazine sulphate, 50% lactose and 25 and 50% avicel pH 101 have been added and it has been observed that 50% lactose prolonged the release of dihydralazine sulphate more than 50% avicel pH 101, whereas 50%

avicel pH 101 released the active principle more quickly than the 25% direct tableting agent (18). In other studies, the absence or presence of 0.75% magnesium stearate as lubricant has not effected the release from HPMC K15M matrices of promethazine HPMC matrix tablets (35) and 75% lactose or calcium phosphate have been added to HPMC matrix tablets of promethazine hydrochloride resulted in an increase in release rates for active substance (36).

In the present study by adding lactose to the tablets coded as T3A and T4A, drug release was determined as 65-70%, but sustained action range was found very low (Fig.3). Although a good sustain action was observed in codes T5A and T6A, drug release reached to only 50-60%. Drug release was also very low in comparison to the other two tablets (T1A, T2A).

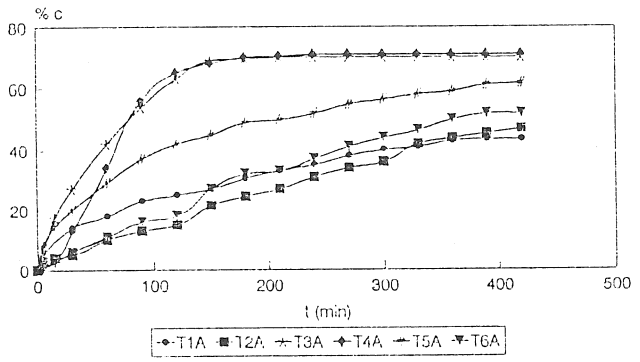

Fig.3. Dissolution profiles of tabletted microcapsule prepared by adding 10% lactose

Dissolution by adding both 10% lactose fast flo and avicel pH 101 resulted in a good sustained action but the drug amount obtained was very low (<50%) (Figs, 4,5).

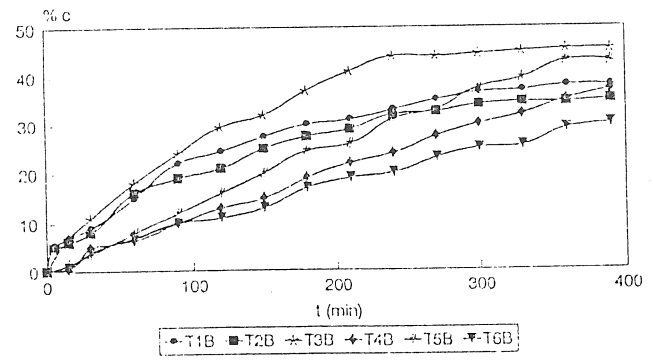

Fig.4. Dissolution profiles of tabletted microcapsules prepared by adding 10% lactose fast flo

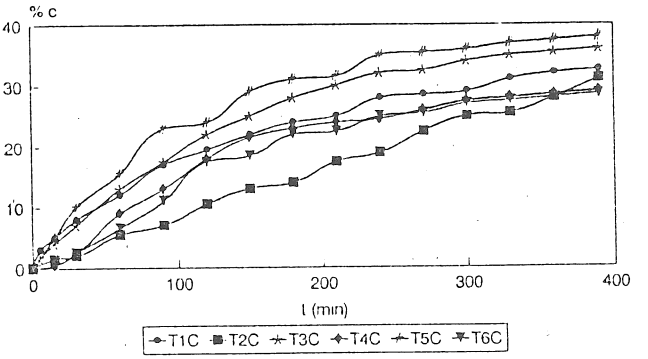

Fig.5. Dissolution profiles of tabletted microcapsules prepared by adding 10% avicel pH 101

According to the obtained results, it was considered to increase the amount of DTA than 25 and 50 per cent of DTA were added to the tablets prepared from microcapsules with 2:1 core:wall ratio and particle size 840-476 μm (Table 4) and dissolution studies were repeated. A satisfactory sustained action was obtained (7 hours) and drug release was increased to 83% in T8C (Fig.6). Drug release of the commercial tablets was 30-60 minutes.

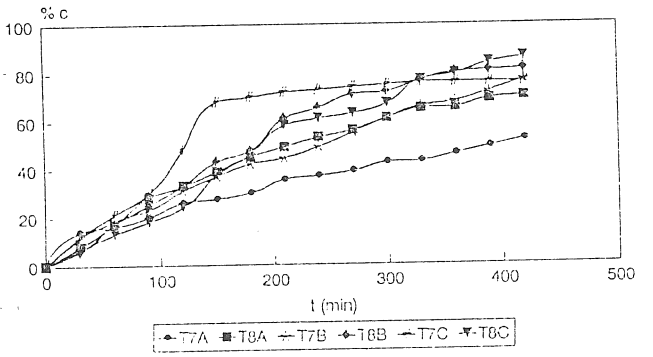

Fig.6. Dissolution profiles of tabletted microcapsules prepared by adding 25 and 50% direct tableting agent

At the end of the dissolution experiments, the tabletted microcapsules used in this study did not disintegrate. This physical property suggests that the release of Nd.HCl from tableted microcapsules is through passive diffusion (37).

According to the kinetic evaluations, the RRSBW distribution was found to be most suitable for defining the release from gelatin capsules and tabletted microcapsules. RRSBW

kinetic propfiles of prepared formulations are illustrated in Fig.7. For the ideal gelatin capsule and tabletted microcapsule, the shape parameters (β) were found as 0.889 and 1.34 respectively, $t_{63.2\%}$ values were 169.89 and 260.55 min.

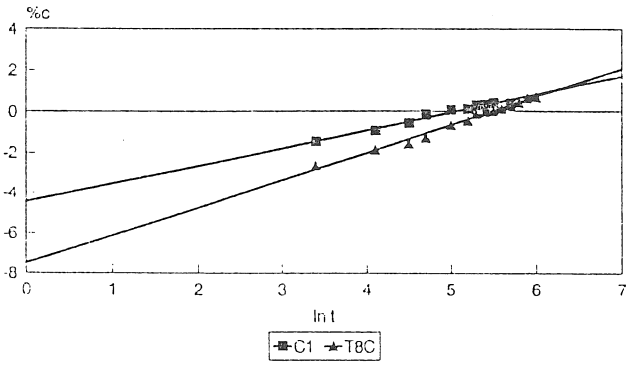

Fig.7. RRSBW distributions of ideal gelatin capsule (C1) and tabletted microcapsule (T8C)

In conclusion, if nicardipine hydrochloride microcapsules are to be prepared in gelatin capsule form, we suggest the microcapsules to be prepared in the form of core:wall 2:1 and particle size >840 μm (as coded C1). If they are to be prepared in the form of a tablet, the microcapsules with a core:wall ratio 2:1 and particle size 840-476 μm by adding 50% avicel pH 101 is suggested (T8C).

The dissolution results obtained at 6-7 hours were evaluated mathematically. For this, the multiple regression model given in Eq.1 was fitted. The estimated model was found to be the best y=-58.371+0.309x+35.459 log t (Eq.2) fitted one for % release of drug from gelatin capsules and tabletted microcapsules without DTA. A three-dimensional response-surface graph for percentage of Nd.HCl released as a function of percentage of drug content and dissolution time was generated by using Eq.2 in order to enable selection of optimum formulation (Fig.8) (p<0.001).

In order to investigate the effect of the drug content and the time on the % drug release of the tablet formulations prepared with DTA, multiple regression model given in Eq.1 has been fitted similar to the one obtained for formulations. The estimated model which is in the form of;

$$y=-18.069-0.067x+23.71 \log t \qquad (Eq.3)$$

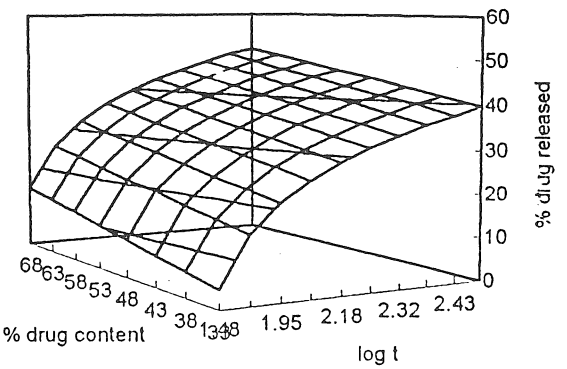

Fig.8. The response-surface graph for percentage nicardipine hydrochloride released from the hard gelatin capsules and tabletted microcapsules as a function of percentage drug content and dissolution time

was found to be best fitted model for % release of drug. By using this equation, % release of Nd.HCl from the tablet formulations containing DTA can be predicted. A three-dimensional response surface graph for percentage of Nd.HCl released as a function of percentage of drug content and dissolution time was generated by using Eq.3 in order to enable selection of optimum formulation (Fig.9) (p<0.001).

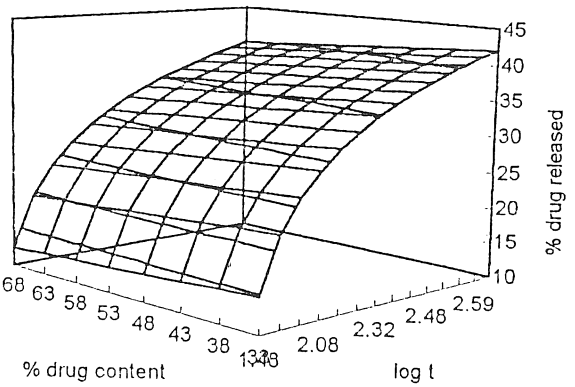

Fig.9. The response-surface graph for percentage nicardipine hydrochloride released from tabletted microcapsules prepared by adding 10% direct tabletting agent as a function of percentage drug content and dissolution time

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