

## FILM COATING PREPARATION OF METOPROLOL TARTRATE MINI-TABLETS AND IN VITRO DRUG RELEASE STUDIES

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### Abstract

*The aim of this experimental work is the obtaining of modified release dosage form, with lag time between 2-6 h, by coating mini-tablets with 3 mm diameter (containing metoprolol tartrate) with insoluble but permeable methacrylate film coating (Eudragit NE 30D) in a fluidized bed system. To achieve this aim, a full factorial experimental design with three factors and three levels was used in order to study the influence of the amount of coating polymer (Eudragit NE 30D), the amount of water-soluble excipient (low viscosity hypoxypopyl methylcellulose HPMC – Methocel E5 LV) and the spraying rate of the polymeric film on the in vitro drug release profile. The amount of HPMC has the most important effect on the metoprolol release for all dissolution time points. Formulations that contain a ratio of 6.5% / 10% Eudragit NE30D and HPMC exhibited lag time of approximatively 4 h, followed by sustained release of about 20 h.*

**Keywords:** modified release, mini-tablets, metoprolol tartrate, experimental design.

## PREPARAREA UNOR MINICOMPRIMATE CU TARTRAT DE METOPROLOL ACOPERITE CU FILME POLIMERICE ȘI STUDII DE CEDARE A SUBSTANȚEI MEDICAMENTOASE IN VITRO

### Rezumat

*Scopul acestei lucrări experimentale este obținerea unor forme cu cedare modificată, cu un timp de latență între 2-6 ore, prin acoperirea unor minicompimate cu diametrul de 3 mm (ce conțin metoprolol tartrat) cu film de acoperire metacrilic insolubil (Eudragit NE 30D), folosind sisteme de acoperire în pat de aer fluidizat. În acest scop s-a folosit un plan experimental cu trei factori și trei nivele, în vederea studierii influenței cantității de polimer pentru acoperire (Eudragit NE 30D), a influenței cantității de excipient solubil în apă (hidroxipropil metilceluloză: HPMC, cu vâscozitate mică – Methocel E5 LV) și a ratei de pulverizare a filmului polimeric, asupra profilului de cedare a substanței medicamentoase in vitro. Cantitatea de HPMC are cea mai mare influență asupra dizolvării metoprololului tartrat la toate punctele de prelevare. Formulările care conțin un raport de 6,5% /10 % Eudragit NE30D și HPMC prezintă un timp de latență de aprox. 4 ore, urmat de o cedare întârziată pe o perioadă de 20 de ore.*

**Cuvinte cheie:** cedare modificată, minicompimate, tartrat de metoprolol, plan experimental.

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## INTRODUCTION

Mini-tablets are tablets having a diameter equal to or smaller than 2-3 mm [1]. Mini-tablets have some benefits which include excellent size uniformity, regular shape and smooth surface, offering an easily coating substrate for modified release purposes [2].

Formulation of the reservoir-type extended release dosage forms consists of coating crystals, granules, pellets and eventually tablets (or mini-tablets) with continuous polymeric film, insoluble in all pH range, but permeable to water and drug solution [3,4]. Among the modified-release oral dosage forms, increasing interest has been shown in systems designed to achieve time-specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed period following administration [5].

These systems constitute a relatively new class of devices, the importance of which is especially connected with recent advances in chronopharmacology. By now it is well-known that the symptomatology of a large number of pathologies, as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform chronotherapy is quite appealing for those diseases [6]. The delay in the onset of release has been achieved through different technology (osmotic mechanism, coating with hydrophilic or hydrophobic layers as semipermeable films, swelling erodible plug sealing of insoluble capsule body and multiple coating technologies [7].

The objective of this work was to obtain reservoir mini-tablets containing metoprolol tartrate and coated with insoluble but permeable methacrylate film (Eudragit NE 30D) as barrier membrane, with lag time of the release between 2-6 h, followed by sustained release.

## MATERIALS AND METHODS

**Materials.** Metoprolol tartrate was received as a gift from Microsin, Romania; polyvinylpyrrolidone – PVP K 30 (BASF Germany); Lactose monohydrate–Pharmatose 200M (DMV-Fonterra, Netherlands); pregelatinised starch–Starch 1500 (Colorcon UK); co-processed excipient - Cellactose 80 (Meggler, Germany), was a gift from Pharmachemicals GmbH, Hamburg; magnesium stearate (Mallinckrodt, USA); silicon dioxide–Aerosil 200(Degussa), Glyceryl behenate-Compritol 888 ATO (Gattefosse, France); talcum (S&D Chemicals UK), Eudragit NE 30D (Evonik, Germany), hydroxypropyl methylcellulose (HPMC)–Methocel type E5 LV (Colorcon), titanium dioxide (S&D Chemicals UK), Opadry OY-S (Colorcon).

**Apparatuses.** Laboratory fluidized bed system Strea 1 (GEA-Aeromatic, Switzerland); tablet press EK-0 (Korsch, Germany); oscillator mill FGS with sieve 0.6 mm (Erweka Germany); dissolution apparatus (Erweka DT800,

Germany); UltraTurax (Janke and Kunkel, Germany), spectrophotometer UV-Vis (Agilent 8453, SUA)

## Experimental Design

In order to study the formulation factors that influence the drug release, especially for drug release modulation, a full experimental design with three factors and three levels was used. The formulation factors (Table I) were: the amount of polymeric film used for coating (Eudragit NE 30D), the amount of pore generating excipient in insoluble polymeric film (low viscosity hydroxypropyl methyl cellulose – Methocel type E5 LV) and the spraying rate of film coating dispersion.

**Table I.** Independent Variables.

Formulation and Process Variable	Symbol	Level		
		-1	0	+1
Percent of Eudragit NE (weight gains)	$X_1$	5	6,5	8
Percent of HPMC (calculated on dry polymer)	$X_2$	10	17,5	25
Spray rate (rpm)	$X_3$	6	9	12

The matrix of experimental design is presented in Table II.

**Table II.** The matrix of the Experimental Design.

Exp No	$X_1$	$X_2$	$X_3$
N1	5	10	9
N2	8	10	9
N3	5	25	9
N4	8	25	9
N5	5	17,5	6
N6	8	17,5	6
N7	5	17,5	12
N8	8	17,5	12
N9	6,5	10	6
N10	6,5	25	6
N11	6,5	10	12
N12	6,5	25	12
N13	6,5	17,5	9
N14	5	12	9
N15	6,5	17,5	9

$X_1$  – percent of Eudragit NE,  $X_2$  – Percent of HPMC,  $X_3$  – Spray Rate (rpm).

The responses were the percent of drug release at different time intervals (Table III).

**Table III.** Dependent Variables ( Responses)

No.	Reponses	Symbol
1	% of the metoprolol tartrate released at 1 h	$Y_1$
2	% of the metoprolol tartrate released at 2 h	$Y_2$
3	% of the metoprolol tartrate released at 4 h	$Y_3$
4	% of the metoprolol tartrate released at 8 h	$Y_4$
5	% of the metoprolol tartrate released at 12 h	$Y_5$
6	% of the metoprolol tartrate released at 16 h	$Y_6$
7	% of the metoprolol tartrate released at 20 h	$Y_7$
8	% of the metoprolol tartrate released at 24 h	$Y_8$

## Software

The experimental design, the calculation of the

coefficients and of the statistical parameters and the evaluation of the fit quality were performed using the Modde for Windows (Version 6.0, Umetrics AB, Umea, Sweden) (MODDE 6, Umetrics Academy, 2001) [8].

#### Mini-tablets preparation

The mini-tablets composition is presented in Table IV.

Granulation process was performed in a fluid bed system Strea 1 (Aeromatic, Switzerland). The mini-tablets were obtained using a KORSCH EK, an eccentric press equipped with die and punches of 3 mm. Seven granulation batches were mixed together and then extragranular ingredients were added, in order to obtain only one batch with the same characteristics for compression (the mini-tablets composition is presented in Table IV).

**Table IV.** Minitablets composition.

		%
IG	Metoprolol tartrate	20.00
IG	Lactose monohydrate	17.38
IG	Povidone K30*	1.40
EG	Cellactose 80	54.72
EG	Colloidal silicon dioxide	1.00
EG	Magnesium stearate	2.50
EG	Compritrol 888ATO	3.00
IG- intra granular ingredient, EG-extra granular ingredient, * aqueous solution 10%;		

#### Characterization of Tablets

The tablets were tested for hardness, friability and uniformity of weight. The hardness of tablets was determined by using the Monsanto hardness tester. Friability and uniformity of weight were determined using official methods [9].

#### Coating of mini-tablets

The mini-tablets were initially seal-coated with an 8% w/w aqueous dispersion of Opadry OY-S to 5% weight gain, in a fluidized bed coating device (Strea 1, Aeromatic Filder). Afterwards they were coated with an insoluble but permeable polymeric film (Eudragit NE 30D) in combination with pores former excipient (HPMC) in different amounts, from an experiment to another, according to the experimental design matrix. The technological parameters during the coating process are shown in Table V.

**Table V.** Process parameters for fluid bed coating.

Process parameters	Seal-coat	Modified release coat
Tablet charge (g)	140	140
Nozzle bore (mm)	0,8	0,8
Atomizing pressure (atm)	1,8- 2	2,2-2,3
Spray rate (g/min)	4-5	Variable *
Inlet air temperature (° C)	63-67	36-42
Outlet air temperature (° C)	45-48	28-34
Fan air (m <sup>3</sup> /min)	8-9	7-9
Preheating time (min)	4	1
Final drying (min) at 40° C (min)	10	10
*as per experimental design equivalent to 6-12 rpm of peristaltic pump.		

#### Dissolution Studies

The dissolution studies were performed using the Erweka DT800 as a dissolution apparatus, in phosphate buffer at pH 6,8 using the paddle method at 100 rpm rotation speed (PhEur7 apparatus 2). Ten mini-tablets (each mini-tablet contains 5 mg of metoprolol tartrate) were put into a vessel with 500 ml dissolution media. At specific time intervals (after 1, 2, 4, 8, 12, 16, 20, 24 hours). 10 ml solutions were withdrawn and 10 ml of fresh medium was added after each sampling. The withdrawn samples were filtered through a 0.45 µm filter and the drug concentration was assayed with the UV spectrophotometer using 274 nm wavelength [10,11]. For each formulation, the dissolution studies were performed thrice.

## RESULTS AND DISCUSSION

#### Mini-tablets characteristics

The results presented in Table VI show that the uncoated mini-tablets have low weight variability, good hardness and did not have friability. These results suggest that mini-tablets have suitable pharmaco-technical properties for coating in fluidized bed device [12].

**Table VI.** Mini-tablets Characteristics.

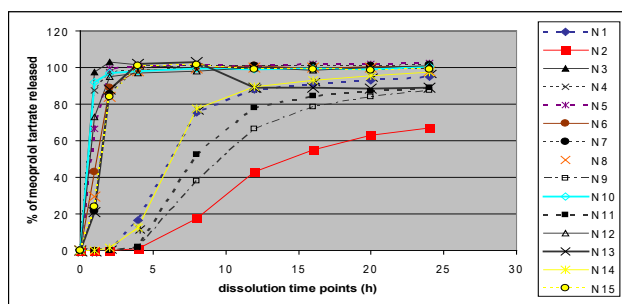
Uniformity of weight (mg)	Hardness	Friability
Mean SD	(N)	(%)
25.52 ± 4.38%	<b>30-40</b>	<b>0.00</b>

#### Experimental Design Analysis. Goodness of Fit

The matrix of the results is shown in Table VII. The dissolution profiles obtained from coated minitables prepared according to the experimental design are shown in Figure 1.

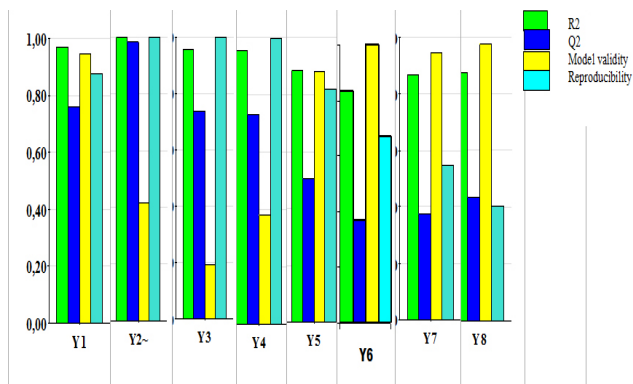
**Table VII.** The matrix of the Responses.

Exp No	Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>3</sub>	Y <sub>4</sub>	Y <sub>5</sub>	Y <sub>6</sub>	Y <sub>7</sub>	Y <sub>8</sub>
N1	0,00	0,00	16,53	75,49	87,81	91,24	93,24	95,20
N2	0,00	0,00	0,80	17,37	42,78	55,02	62,99	67,25
N3	97,38	103,01	101,73	99,65	100,20	100,13	100,23	100,24
N4	87,59	97,63	98,65	99,21	99,69	99,00	98,52	99,38
N5	66,68	99,26	101,09	101,39	100,96	101,90	102,16	102,62
N6	42,86	89,14	98,26	99,51	101,19	99,40	100,29	100,52
N7	21,58	85,45	100,04	100,80	101,17	100,92	100,91	101,30
N8	29,27	84,15	98,22	99,62	100,02	99,83	100,13	98,00
N9	0,00	0,00	1,32	37,95	66,27	78,60	83,86	87,39
N10	92,00	97,23	98,00	99,66	98,76	99,45	98,92	100,62
N11	0,00	0,00	1,79	52,34	77,86	84,75	87,19	89,09
N12	73,20	95,12	97,00	98,00	99,78	98,32	100,02	101,20
N13	21,05	87,90	101,85	102,96	89,05	88,90	88,68	88,94
N14	0,00	1,37	12,35	77,46	89,59	92,79	95,41	97,32
N15	24,05	83,90	100,85	101,56	99,04	98,96	98,68	98,94



**Figure 1.** The percent of the metoprolol tartrate released from the experimental formulation (N1-N15 see Table II) at different dissolution time points.

In order to fit the experimental data with chosen experimental design and the calculation of the statistical parameters, the statistical module from Modde 6 software was used. To check the validity of the experimental design the following statistical parameters were determined:  $R^2$ ,  $Q^2$  and Anova test.  $R^2$  represents the fraction of variation of the response explained by the model and  $Q^2$  represents the fraction of variation of the response that can be predicted by the model. Both  $R^2$  and  $Q^2$  values are numbers, usually between 0 and 1. Values close to 1 for both  $R^2$  and  $Q^2$  indicate a very good model with excellent predictive power.  $R^2$  and  $Q^2$  provide the best summary of fitting the model [13]. The results obtained after the fitting and the statistical parameters calculation using data obtained from the experimental design, are shown in Figure 2.



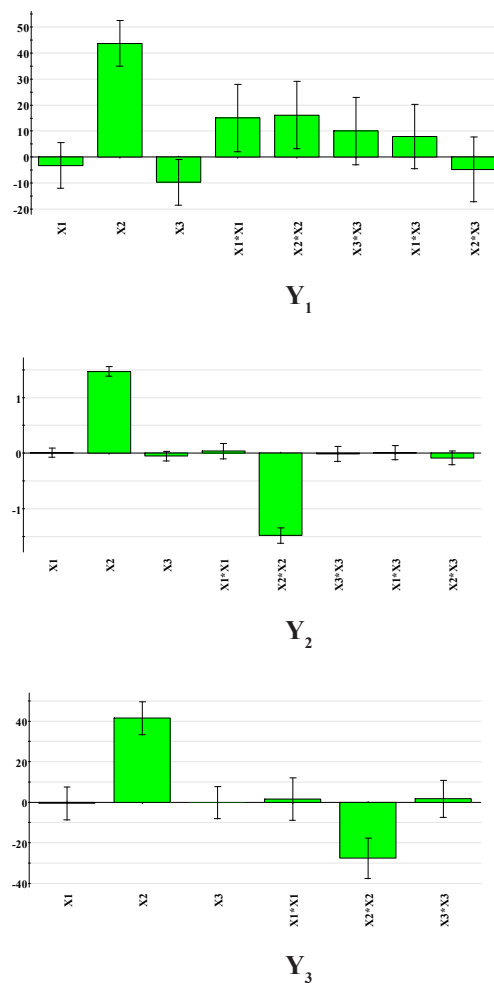
**Figure 2.** The fitting of the experimental data with the chosen model: % of the metoprolol released:  $Y_1$  – 1 h,  $Y_2$  – 2 h,  $Y_3$  – 4 h,  $Y_4$  – 8 h,  $Y_5$  – 12 h,  $Y_6$  – 16 h,  $Y_7$  – 20 h,  $Y_8$  – 24 h.

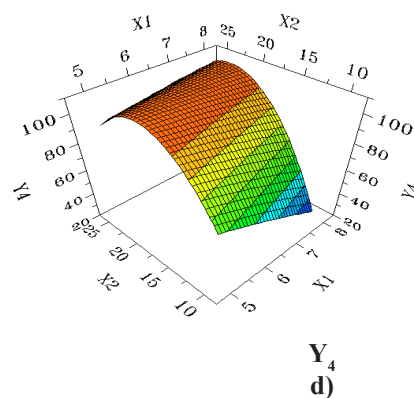
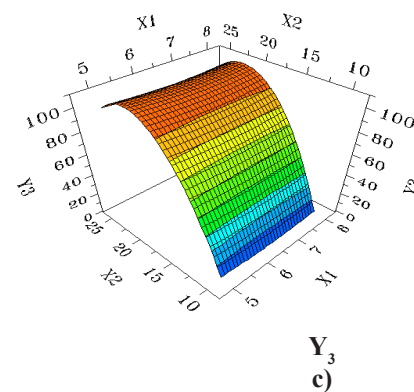
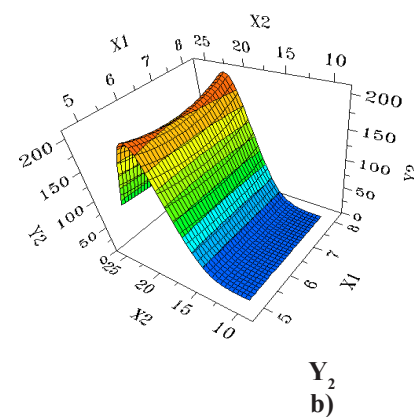
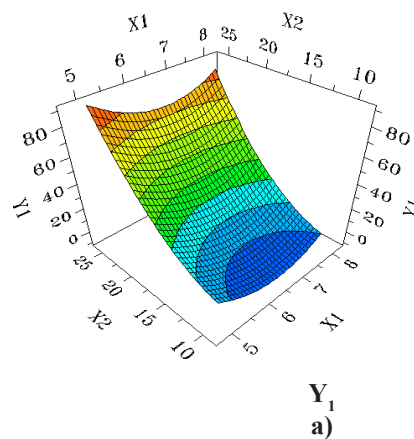
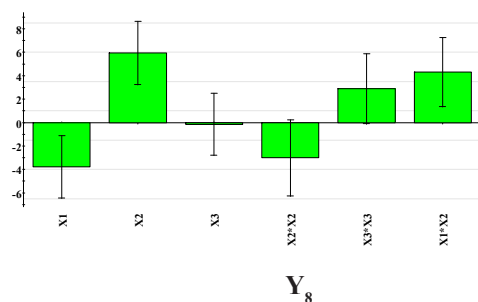
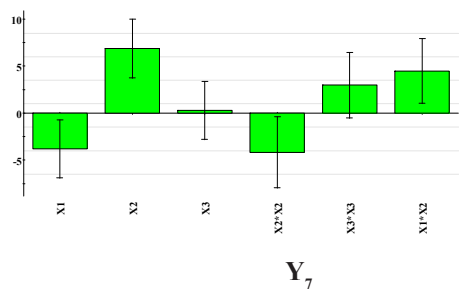
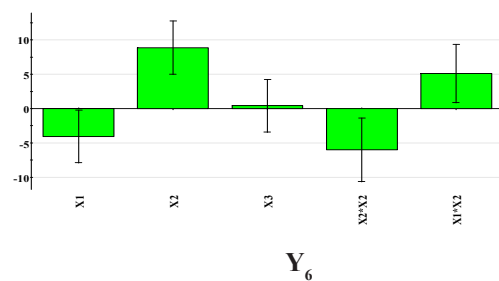
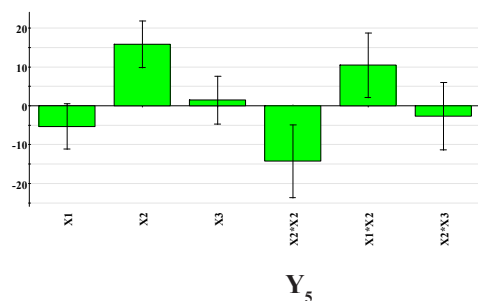
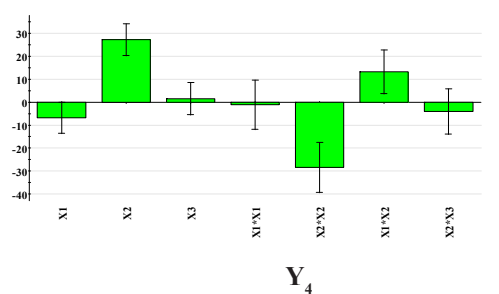
The fitting results are satisfactory for all responses. ANOVA test (analysis of variance) shows if the variance of results is determined by modifications of the formulation factors or represents a variance determined by experimental errors (MODDE 6, Umetrics Academy, 2001). The results of ANOVA test shown that the experimental data obtained for  $Y_1$ - $Y_8$  responses were good ( $p$  for model was lower than 0,05 and  $p$  for residual was higher than 0,05) for all responses.

### Experimental design analysis

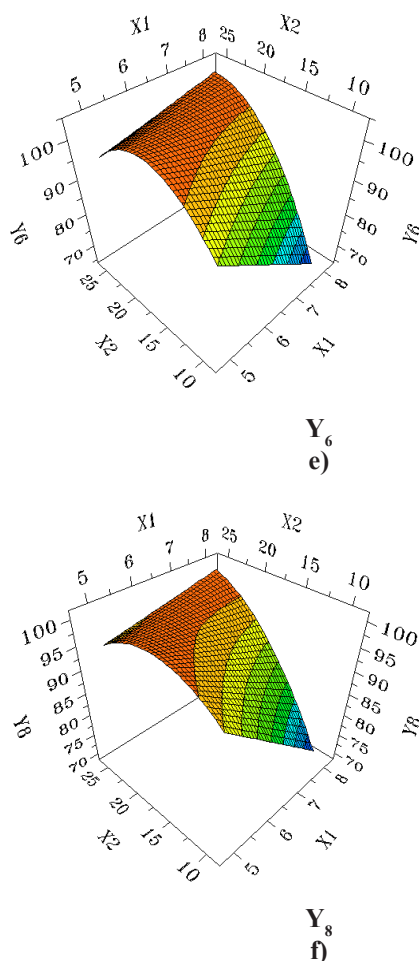
Eudragit NE 30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate widely used to obtain reservoir type extended release formulation. It is insoluble but it can swell in water and has low permeability [14]. A water soluble additive may be included in the film to increase the permeability of the membrane when the product is exposed to an aqueous environment during the dissolution phase [15,16]. The addition of a water-soluble additive may improve the reproducibility of release rate properties and compensate for variability in processing conditions [17,18]. For these reasons an easy soluble polymer (low viscosity HPMC – Methocel E5 LV) was used as pore generating excipient. A three-factor, three-level full experimental design was applied to construct a second-order polynomial model describing the effect of the formulation factors on the characteristics of the product.

The amount of HPMC has the most important effect on the metoprolol release at all dissolution time points. The increase of the amount of HPMC increases the release of metoprolol tartrate for all dissolution time points (Fig 3, Fig 4).





**Figure 3.** The influence of the formulation factors on the metoprolol release at different time interval, Y- % of the metoprolol released : Y<sub>1</sub> – 1 h, Y<sub>2</sub> – 2 h, Y<sub>3</sub> – 4 h, Y<sub>4</sub> – 8 h, Y<sub>5</sub> – 12 h, Y<sub>6</sub> – 16 h, Y<sub>7</sub> – 20 h, Y<sub>8</sub> – 24 h, X1-Percent of Eudragit NE, X2 - Percent of HPMC, X3 – spray rate.



**Figure 4.** The influence of the formulation factors on the metoprolol release at different time intervals, Y - % of the metoprolol released : a)  $Y_1$  - 1 h, b)  $Y_2$  - 2 h, c)  $Y_3$  - 4 h, d)  $Y_4$  - 8 h, e)  $Y_6$  - 16 h, f)  $Y_8$  - 24 h; X1-Percent of Eudragit NE, X2-Percent of HPMC, X3 - spray rate.

The amount of the coating polymer, Eudragit NE 30D is less significant for the drug release than the amount of HPMC and the influence is different depending on the dissolution time points. In the first 4 h the increase of the percent of Eudragit NE 30D did not have influence on the release of the drug, but after that, the increase of the percent of the polymer reduced the percent of metoprolol released (Fig 3, Fig 4). The spray rate of the film coating dispersion did not have influence on the release rate of the drug (Fig 3).

Formulations that contains higher quantities of HPMC - Methocel E5 LV (17,5- 25% w/w) as pore generating agent in polymeric film showed a burst drug release, while the formulation that contains lower quantities of HPMC (10-12%), exhibited lag time of about 4-5 hours, followed by a sustained release of about 20 h (formulations: N1, N2, N9, N11, N14).

The enhanced dissolution rate, as result of increasing in the amount of pore generating agent, was probably due

to an increased permeability of barrier membrane.

The lag time prior to drug release or delayed release is meant to deliver the metoprolol tartrate after a programmed period following administration. Such dosage forms, when administered at bed time, would enable maintaining drug plasma concentration at a level potentially beneficial in minimizing the occurrence of heart attacks in the early hours of the morning [6].

## CONCLUSIONS

Based on the foregoing, it can be concluded that modified release of metoprolol tartrate mini-tablets with application in chronotherapy (lag time of the release approximatively 4 h) was obtained if the ratio of Eudragit NE30D and HPMC is carefully selected. In this regard, an optimum Eudragit NE30D and HPMC ratio of 6.5% /10% for the coating polymer was found, in order to obtain the desirable lag time and minimum 80% drug released in 24 hours.

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