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DELIVERY OF NEBIVOLOL HYDROCHLORIDE FROM IMMEDIATE RELEASE TABLETS

Zahraa Khalaf[1], Simona Ardelean[2], Doina Drăgănescu[1], Monica Ardelean[2], Dumitru Lupuleasa[1]
[1] „Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest
[2] „Vasile Goldiș" Western University of Arad, Faculty of Pharmacy, Arad, Romania

ABSTRACT: The paper presents the results of our study regarding 9 formulations with nebivolol 10 mg with immediate release. The solubility of nebivolol hydrochloride was determined in various aqueous solutions and buffer (HCl pH=2). The solubility study was conducted by taking excess amounts of the drug in solution. In vitro dissolution profiles showed a rapid release, approaching 10% of the declared content of nebivolol hydrochloride, towards the end of the test period.

Keywords: nebivolol hydrochloride, immediate release tablets, dissolution tests, USP 34

INTRODUCTION:

Immediate release tablets represents the main pharmaceutical form for oral administration of a drug.(1) The absorption processes are dependent on the one hand by the disintegration/disaggregation of the vehicle, correlated with motility and particularities of the biological fluids, and on the other hand by the solubility of the active substances. It must be underlined the fact that the actually methodology of the evaluation of the dissolution profiles *in vitro* was developed as a result of the impact awareness that changes in composition, qualitative and/or quantitative may have on the performance of biopharmaceuticals. (Mircioiu *et al.*, vol. 1 2008; Mircioiu *et al*., vol. II 2008,)

Hypertension is a widespread condition of the high systemic arterial pressure and it is an important factor for the extension of cardiovascular diseases. It also represents one of the main causes of the global mortality in accordance with a test elaborated by the World Health Organization. Many patients have additionally risk factors, like diabetes or a history of cardiovascular disease. Thus, the β-blockers represent a important tool used in treatment of hypertension and the medication that combines more actions are becoming increasingly popular. Among these, belongs also Nebivolol, a relatively new product, which blends harmoniously the β-adrenergic blocker effect with the vasodilator one.

Nebivolol has the greatest affinity for the β_1-receptors and, most interesting, it substantially improves endothelial dysfunction through its strong stimulatory effect on the activity of endothelial nitric oxide synthesis and through his antioxidative properties. Since the activity of endothelial damage is seen as a major cause in the pathophysiology of hypertension, coronary heart disease and congestive heart failure, endothelium-agonistic properties of nebivolol suggest that the drug may provide additional benefits compared to other β-receptor blockers. Clinically, this compound was shown to have antihypertensive and anti-ischemic effects as well as beneficial effects on haemodynamics and prognosis in patients with chronic congestive heart failure. All this contributes to its effectiveness as a medicine and improves its tolerability.

For many drugs, especially for those who are poorly soluble in gastric fluid, as the nebivolol, the rate-limiting step for the absorption process is the dissolution rate, so that a determination of this parameter may be useful to compare the bioavailability. (Khan, 1975; Siewert *et al.*, 2003)

Dissolution is the process by which a solid solute enters a solution. The pharmaceutical industry can be defined as the amount of drug substance that goes in solution per unit time under standardized conditions of the liquid / solid interface, temperature and solvent composition. (Popovici *et al.*, 2008; Popovici *et al.*, 2009). Dissolution is considered to be one of the most important tests performed for the quality control of pharmaceutical forms and continuously develops in order to provide information about bioavailability. Drug Dissolution behaviour has a significant effect on his pharmacological activity. (Tsong *et al.*, 2003)

In fact, a direct relationship between the *in vitro* dissolution rate of many drugs and their bioavailability has been demonstrated and is generally reported by the correlation between *in vitro* and *in vivo*.

Tablets due to a strong compression or to a high content in thickener employed in the granulation may be too compact, and that cause their very slowly disintegration in the gastrointestinal tract. (Khan *et al.*, 1972)

If the disintegration doesn't take place in a certain time, the tablets are crossing the digestive tract and they are eliminated. The drug could not do its intended action.

To facilitate tablet disintegration in the gastrointestinal fluid, among other methods it is used the introduction of disaggregated excipients. They work by different mechanisms: swelling (starch, MC, CMC, agar-agar, alginic acid); the production of gaseous substances (tartaric acid, citric acid, calcium carbonate, sodium bicarbonate); by melting (eutectic forms or mixtures which melt at body temperature); by enzymatic destruction of the binder. (Popovici *et al.*, 2008; Popovici *et al.*, 2009; Saramet *et al*., 2013).

Correspondence: Doina Drăgănescu, Carol Davila University of Medicine and Pharmacy, 6 Traian Vuia St., Bucharest, Romania. Tel: +40-(21)-3180747, email: doinadraganescu@yahoo.com
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MATERIALS AND METHODS:

In vitro dissolution testing procedure

In view of the things discussed before, were several formulations of immediate release tablets of nebivolol hydrochloride, 10 mg, in order to improve the bioavailability and the therapeutic effect by increasing the amount of drug released in a shorter time interval.

In this regard, in a first stage, it was analysed the influence of super disintegrants cross povidone and cross carmellose sodium on the tablet disintegration and on the release of the drug.

For this purpose 9 different formulations with nebivolol hydrochloride 10 mg and immediate release were analyzed; the tablets were produced via wet granulation. For all 9 formulations were varied the amount and the type of superdisintegrant.

The formulations development is shown in the following table:

Table I.

Qualitative and quantitative composition (mg / cpr) of tablets containing nebivolol 10 mg, obtained by wet granulation

Ingredients (mg)	Formulation code								
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Nebivolol HCl	10,90	10,90	10,90	10,90	10,90	10,90	10,90	10,90	10,90
MCC PH 101 (microcrystalline cellulose pH 101)	54,46	55,65	55,35	58,30	52,90	53,15	54,20	56,00	55,90
Mannitol	30	36	45	56	60	65	72	68	68
SLS (sodium lauryl sulphate)	-	0,80	0,90	0,90	-	0,50	0,70	0,20	0,60
Lactose Monohydrate	72	62,4	46	30	28	22	8,0	14	15
Pre-Gelatinized starch	48	45	48	50	54	54	60	56	56
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
HPMC E15 CPS	3	3,35	4,4	5	5	4	6	5	4
CCS (cross carmellose sodium)	11	12	13	13	12	16	16	15	14
CP (crosspovidone)	-	3	4,5	5	2	1	-	-	-
Magnesium stearate	10	10	10	10	12	12	12	12	12
Aerosol	0,72	0,90	0,95	0,90	0,90	0,95	1,20	1,20	1,20
Polysorbate 80	-	-	-	-	2,20	1,00	-	1,20	1,40
Total weight	240	240	240	240	240	240	240	240	240

Dissolution studies were carried out in accordance with the USP 34 monograph, employing USP – II paddle method, using a dissolution tester Erweka DT device 800, produced by Erwecka GmbH, Germany.

The solubility of nebivolol hydrochloride was determined in various aqueous solutions and buffer (HCl pH = 2). The solubility study was conducted by taking excess amounts of the drug in 10 ml of the solution and the solutions were kept in the water bath shaker for 72 hours. Finally, the solution was filtered and diluted with sufficient amount of the same solvent. The absorbance of the solution was determined at 269 nm. The results are presented in the following table:

Table II.

Solubility study data of Nebivolol Hydrochloride in various solvents and buffers

Test no.	Name of solvent/buffer	Concentration (mg/ml) (±SD), n=3
1	Water	0,0017 (0,001)
2	Hydrochloric acid buffer pH 1,2	1,2234 (0,159)
3	Phosphate buffer pH 6,5	0,0012 (0,000)
4	Acetate buffer pH4,8	0,1690 (0,026)
5	PEG	0,9102 (0,003)
6	DSMO	0,4567 (0,002)
7	Methanol	0,0814 (0,001)

From the table above, it can be seen that the maximum concentration of solubilised nebivolol is obtained when using HCl buffer pH 1.2 (acid medium) and the minimum when using pH 6.5 phosphate buffer (neutral or slightly basic).

Release profiles of the drug in the studied tablets

To observe much better the percentage variation of dissolved nebivolol hydrochloride at the studied time points, the data obtained was gathered in the following table (Table III) and the dissolution profiles % were reflected in Figure 1:

Table III.

Dissolution profiles of immediate release tablets of nebivolol hydrochloride and of the Innovator in HCl buffer (pH 2)

Formulation	Time (min)			
	10	20	30	45
F1	62,61	75,27	86,36	95,55
F2	54,86	84,48	93,23	93,80
F3	49,84	76,73	89,75	91,08
F4	36,64	60,54	76,00	91,66
F5	56,27	62,20	76,21	85,72
F6	38,21	47,72	73,17	90,55
F7	80,00	85,16	93,83	97,95
F8	54,76	89,43	93,39	93,53
F9	38,80	60,58	84,31	94,76
Innovator	71,37	76,05	86,05	96,22

RESULTS AND DISCUSSION:

The influence of formulation on the in vitro release profiles of nebivolol hydrochloride

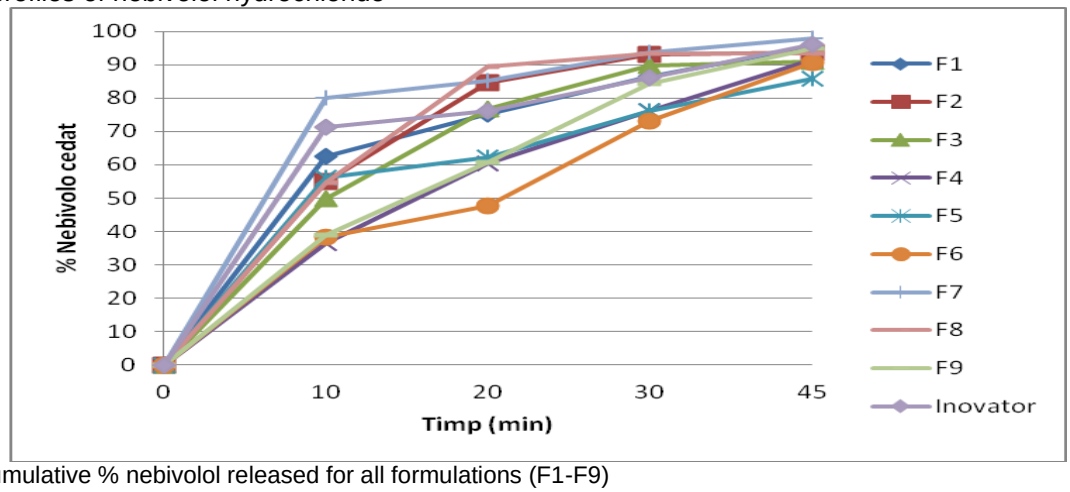

Fig. 1. Cumulative % nebivolol released for all formulations (F1-F9)

The analysis of the dissolution profiles for the 9 proposed formulas compared with the innovator profile shows the following:

- After 10 minutes, the best assignment is recorded in the F7 formulation (80.00%) superior to the innovative (71.37%) and the lowest in the F7 formulation (36.64%);
- After 20 minutes, the best disposal is recorded in the F8 formulation (89.43%) and F7 (85.16%), superior to the innovative (76.05%) that is lower even than the F2 (84.48%) and F3 (76.73%);
- After 30 minutes, of best release profiles is recorded for F7 (93.83%), F8 (93.39%) F2 (93.23%) and F3 (89.75%), superior to the innovative (86.05%).
- At the end of the test interval (45 minutes) best profile is recorded for the F7 (97.95%), followed by the innovative (96.22%) and F1 (95.55%).

In vitro dissolution profiles showed a rapid release, approaching 100% of the declared content of nebivolol hydrochloride, towards the end of the test period (45 minutes). Considerable differences are recorded in the first 20 minutes.

From the analysis of obtained data, it can be seen that Formulation 7 (16 mg croscarmellose) is leading to maximum delivery, right from the start.

Therefore, it will be taking into consideration for the release kinetics and stability studies.

The release profile of this formula, which is the best, is shown in the following chart

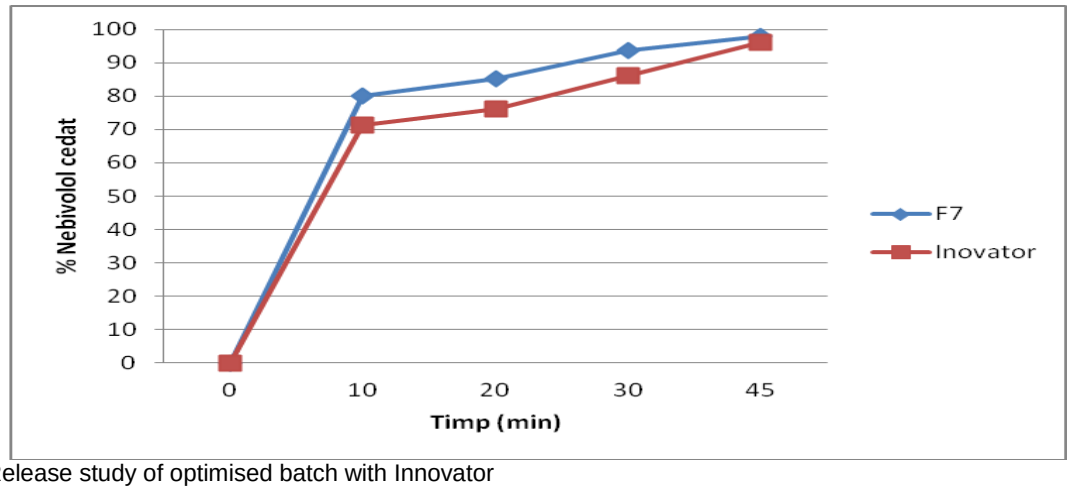

Fig. 2. Release study of optimised batch with Innovator

The results of this study confirm our initial hypothesis, namely that super-disintegrant excipients are very important in nebivolol release from immediate-release formulations.

This formulation can be considered as an ideal candidate for the exemption of the *in vivo* evaluation.

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