

THE OPTIMIZATION OF PROLONGED RELEASE MATRIX TABLETS WITH BETAHISTINE DIHYDROCHLORIDE - Part I

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Abstract

Hydrophilic matrix tablets with betahistine dihydrochloride and different types of hydroxypropyl methylcellulose (HPMC) with different viscosity degrees were compressed by wet granulation, in order to obtain a prolonged release of the active substance. The effects of the different sorts of HPMC, the pharmaceutical properties (hardness, friability and their influence on *in vitro* release of the active substance), were studied. The results showed that the percent of HPMC and the degree of viscosity have the highest effect on the release of betahistine dihydrochloride.

Rezumat

Au fost realizate comprimate de tip matriță hidrofilă conținând diclorhidrat de betahistină și diferite tipuri de hidroxipropilmetil celuloză (HPMC) cu diferite grade de vâscozitate, prin metoda granulării umede, pentru a obține o eliberare prelungită a substanței active. Au fost studiate efectele diferitelor tipuri de HPMC și proprietățile farmaceutice ale comprimatelor (duritate, friabilitate și influența lor asupra eliberării *in vitro* a substanței active). Rezultatele au arătat că procentul de HPMC din comprimate și gradul de vâscozitate au cel mai mare efect asupra eliberării diclorhidratului de betahistină.

Keywords: betahistine dihydrochloride, hydroxypropyl methylcellulose (HPMC), prolonged release matrix tablets

Introduction

Over the last years, pharmaceutical preparations with prolonged release were more and more used, due to their advantages:

- they reduce the occurrence of adverse reactions that are caused by a too high level of active ingredient in plasma, or the lack of therapeutic effect, due to a plasma concentration of active ingredient that is too low;
- they ensure the constant release of the active ingredient in the organism between two administrations;
- decrease of administration times in case of chronic patients [1].

We studied the influence of some of the formulation factors upon the dissolution profile of the active ingredient from tablets containing betahistine dihydrochloride.

The first objective of this paper was to prepare tablets with prolonged release in form of matrix and to define their pharmaceutical properties. One of the excipients that are commonly used on large scale in the formulation of prolonged release tablets in matrix form is hydroxypropyl methylcellulose, of different viscosity degrees [1,2,9,10].

In this study we tested four types of hydroxypropyl methylcellulose (HPMC) with different viscosity degrees.

The pharmaceutical substance chosen, betahistine dihydrochloride, is a synthetic analogue of histamine [3,4,5,6,7].

Betahistine dihydrochloride, is indicated in the treatment of vertigo, associated with functional impairment of the vestibular system in the symptoms' context of the Ménière disease. This disease appears mainly in elderly, the treatment being of long-term; thus a perfect tolerance of the product is required.

Due to the fact that betahistine dihydrochloride is highly soluble in water and the halftime is short (3 hours) – which lead to frequent administrations (2 to 4 administrations per day, depending on the dosage used - 8mg/24mg), a pharmaceutical form that ensures a prolonged and uniform dissolution of the active ingredient is very useful, in the same time reducing the risk of adverse reactions.

Betahistine dihydrochloride is very soluble in water and has a good permeability, therefore this drug can be an appropriate candidate for prolonged release preparations.

Materials and methods

Materials

The Betahistine dihydrochloride (Sifavitor- Italy) used was a white to slightly yellow crystalline powder, very soluble in water.

HPMC 100/4000/15000/100000 (hydroxypropyl methylcellulose), supplied by Shinetzu – Japan, has been used, as a retarding excipient in the tablets.

Microcrystalline cellulose - Vivapur 102 (JRS Pharma, Germany), was used as filler in the studied formulations.

For the stability of the active substance, in time, citric acid (Chemopar, Romania) was used as antioxidant.

As gliding and lubricant agents there were used talcum (Luzenac, Italy) and fumed silica - Aerosil (Evonik, Germany).

Methods

Preparation of the matrix tablets

The tablets were obtained by wet granulation, using a mixture of matrix forming substance with different viscosities, in equal quantities (20% and 30%). The steps of the granulation process were the following: mixing, granulation-drying (Fluid Bed Dryer - IMA), lubrication, compression in the rotating tableting machine (Manesty).

The weight of each of the obtained tablets was around 300 mg having a hardness over 100 N force. Each tablet contains 32 mg betahistine hydrochloride as active substance. The tablets formulations analyzed in this study were noted B1 - B6 and are presented in Table I.

Table I

The formulation of betahistine dihydrochloride matrix tablets

	B1	B2	B3	B4	B5	B6
Raw materials	mg/tb.	mg/tb.	mg/tb.	mg/tb.	mg/tb.	mg/tb.
Betahistine dihydrochloride	32.00	32.00	32.00	32.00	32.00	32.00
Anhydrous citric acid	6.00	6.00	6.00	6.00	6.00	6.00
HPMC 100	60.00	-	-	90.00	-	-
HPMC 4000	60.00	60.00	-	90.00	90.00	-
HPMC 15000	-	60.00	60.00	-	90.00	90.00
HPMC 100000SR	-	-	60.00	-	-	90.00
Microcrystalline cellulose 102	126.00	126.00	126.00	66.00	66.00	66.00
Talcum	15.00	15.00	15.00	15.00	15.00	15.00
Colloidal anhydrous silica dioxide	1.00	1.00	1.00	1.00	1.00	1.00
Alcohol	72.00	72.00	72.00	72.00	72.00	72.00
Purified water	8.00	8.00	8.00	8.00	8.00	8.00
Total	300.00	300.00	300.00	300.00	300.00	300.00

The tablet hardness was performed on 10 tablets of each type, using the Tablet Hardness Tester (TABLET TESTER 8 M - DR.SCHLEUNIGER, Swiss) in accordance with the Romanian Pharmacopoeia 10th Ed. and European Pharmacopoeia. The determination of the friability was performed on 20 tablets of each type, using a Friabilator (EF-2 - ELECTRO LAB, INDIA) in accordance with the Romanian Pharmacopoeia 10th Ed.

***In vitro* release studies**

The dissolution test has been carried out in accordance with the Romanian Pharmacopoeia 10th Ed. and European Pharmacopoeia – method 1, using SR 8 Plus Dissolution Testing Station (HANSON RESEARCH – USA). The determination was performed under the following conditions:

- dissolution medium: distilled water;
- medium volume: 900 mL;
- temperature: $37 \pm 0.5^\circ \text{C}$;
- speed rotation: 75 rpm;
- test duration: 10 hours.

The samples have been collected at predetermined time intervals (1, 2, 3, 4, 5, 6, 8, 10 hours) and the assay of betahistine dihydrochloride has been performed under European Pharmacopoeia 6th Ed. conditions. At each time interval samples of 50 mL were withdrawn from the dissolution media, immediately filtered through a $0.45 \mu\text{m}$ filter and replaced with fresh media to maintain a constant volume across the experiment.

The assay was performed in UV, at $259 \pm 2\text{nm}$ wavelength.

The *in vitro* studies were performed in triplicate.

Results and discussion

Evaluation of matrix tablets

We studied the influence of different types of HPMC within the formulation. For this, we studied the hardness and the friability of the tablets. We also evaluated the *in vitro* release profile of the active substance from the matrix tablets.

The mean values of hardness and friability of 10 determinations for each formulation are shown in Table II.

Table II

The influence of HPMC concentration (%) and HPMC type on the hardness and friability of the matrix tablets

Formulation	Hardness [N]	Friability [%]
B1(20% HPMC 100 +20% HPMC 4000)	101.2	0.78
B2(20% HPMC 4000 +20% HPMC 15000)	108.4	0.54
B3(20% HPMC 15000 +20% HPMC 100000)	111.2	0.49
B4(30% HPMC 100 +30% HPMC 4000)	104.5	0.65
B5(30% HPMC 4000 +30% HPMC 15000)	110.5	0.54
B6(30% HPMC 15000 +30% HPMC 100000)	114.6	0.51

The values obtained show that the B3 and B6 formulas which are produced with a mixture of two types of HPMC with a higher degree of viscosity have a greater hardness and a lower friability.

The friability of all the formulations is less than 1%, which is a good value [8]. For all the tablets studied, the hardness is over 100 kp, which indicates that they have good hardness. Regarding the percentage of HPMC in the tablets, the ones obtained with a mixture of HPMC in percentage of 20% have a lower resistance than the ones obtained with the same mixture of HPMC in a percentage of 30%.

***In vitro* release study of betahistine dihydrochloride**

The mean values of the 3 determinations for each formulation are shown in Table III.

Table III

The influence of HPMC concentration (%) and HPMC type on the *in vitro* release of the matrix tablets

Percentage of active substance (betahistine dihydrochloride) from the tablets (%)								
Formulation	1h	2h	3h	4h	5h	6h	8h	10h
B1	42.16	60.69	70.58	76.77	84.55	93.24	100	100
B2	33.51	50.24	68.28	73.15	82.87	90.75	100	100
B3	29.24	46.41	64.57	69.14	80.27	88.195	96.78	100
B4	34.18	55.28	64.26	73.35	82.47	91.57	100	100
B5	22.45	37.48	53.54	67.78	76.48	84.59	94.24	100
B6	18.93	39.21	47.85	64.89	73.86	81.95	87.58	98.47

The release profiles of betahistine dihydrochloride from the formulated experimental release matrix tablets are shown in figure 1.

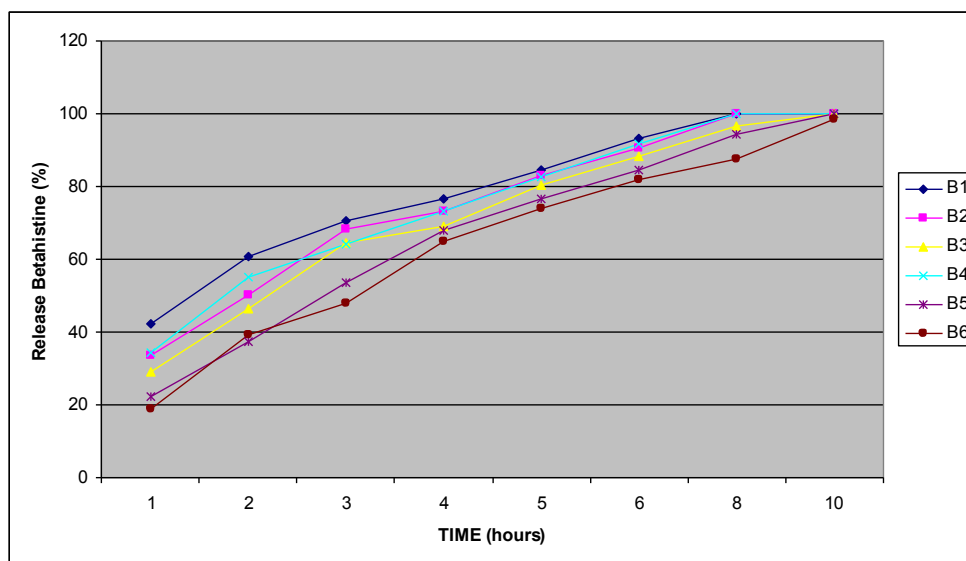


Figure 1

Release profiles from the studied prolonged release tablets

From these release profiles we can observe that the increase of the HPMC percentage within the formulation has a significant influence on the prolongation of the release of betahistine hydrochloride from the tablet. The best results were obtained in the case of formulas B2, B3, B5 and B6, where different types of HPMC with high viscosity degrees were used. The increase of 50% for the quantity of HPMC used leads to a delay rate in the release of active substance of 33 – 35% (in the first hour) and 6 – 9% (after 8 hours).

Within our experiments we also registered results when betahistine dihydrochloride was released faster, in formulas B1 and B4, when types of HPMC with low viscosity grades were used, and the increase of HPMC quantity by 50% didn't translate into a significant delay in the release of the active substance.

The use of HPMC with higher viscosity degrees had a significant influence on the prolongation of the release of betahistine hydrochloride from the tablets. We observed that in the B6 formula, compared with B1, there is a delay in the release of the active ingredient ranging between 55% (in the first hour) and 12% (after 8 hours).

Conclusions

We developed prolonged release matrix tablets containing betahistine dihydrochloride by wet granulation.

We have found that the increase of the percent of mixture of two types of HPMC with a higher degree of viscosity had a significant influence on the prolongation of the release of betahistine dihydrochloride from the tablet.

We observed that, regardless the degree of viscosity of HPMC and the quantity used in the formulation, we couldn't obtain a delay in the release of the active ingredient lower than 80% after 8 hours. This may be explained by the very high solubility of betahistine dihydrochloride in water.

We will continue our research, using other excipients and techniques for retarding the release, in order to obtain a pharmaceutical formula with betahistine dihydrochloride that has a controlled release over 12 hours.

References

1. Popovici I, Lupuleasa D, Tehnologie Farmaceutica Vol 3, Editura Polirom, 2009, 627 – 640
2. Tiwari S.B., Rajabi-Siahboomi A.R., Modulation of drug release from hydrophilic matrices, *Pharmaceutical Tehnology Europe*, September 2008, 24-31
3. Nelson E., Sallee F, Treatment methods employing histamine H3 Receptor antagonists, including betahistine, World Intellectual Property Organization, 2007
4. Lacour M., Sterkers O., Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action, *CNS Drugs*, 2001, 15(11): 853-870
5. Gater P.R., Webber S.E., Gui G.P., Jordan C.C., Hayes N.A., Ashford J.J., Foreman J.C., Some studies of the action of betahistine at H1 and H2 receptors for histamine, *Agents and actions*, 1986, 18(3-4): 342-350
6. Kantor I., Jurkiewicz D., Assessment of betahistine dihydrochloride effectiveness in the treatment of vertigo of a different aetiology based on videonystamography test results, *Polski merkurius lekarski: organ Polskiego Towarzystwa Lekarskiego*, 2006, 20(117): 318-321
7. Dutia M.B., Betahistine, vestibular function and compensation: in vitro studies of vestibular function and plasticity, *Acta otolaryngologica*, 2000, 544:11-14
8. ***European Pharmacopoeia 6.0. Edition 2008: 278 – 279
9. Iovanov R., Tomuta I., Leucuta S., Influence of some formulation factors on the release of felodipine from extended release hydrophilic matrix tablets *Farmacia*, 2009, 57,5, 582-589
10. Ochiz L., Stoleriu I., Moscalu M., Popa G., Spac A., Popovici I., Investigations on the *in vitro* release mechanism of sodium alendronate from hydrophilic matrix tablets *Farmacia*, 2010, 58,6, 795-805

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