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ORIGINAL RESEARCH

Preformulation Studies of Transdermal Therapeutic Systems Containing Betahistine

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ABSTRACT

Betahistine has been used in the treatment of diseases accompanied by impaired peripheral circulation, e.g. Ménière's syndrome, to reduce the frequency of episodes of vertigo and tinnitus. The drug has a short half-life and should be taken three times daily. Its contraindication in patients with peptic ulcer history and the difficulty of frequently dosing requires administration ways other than the oral route. The aim of this study was to prepare transdermal therapeutic system formulations containing betahistine by using synthetic and FDA approved polymers, Eudragit RL 100 and Eudragit RS 100. All the ingredients were evaluated for their excipient-drug compatibility, using Differantial Scanning Calorimetry (DSC) tests. Formulations with different excipient ratios were prepared and evaluated for their macroscopic properties (general appearance, homogeneity, flexibility, transparency and color). Results indicated that there was no incompatibility between drug and excipients. Excipient ratios were optimised according to the macroscopic properties of the formulations.

Key words: Betahistine, transdermal therapeutic system, DSC, Eudragit

INTRODUCTION

Ménière's disease is a disorder of the inner ear which results in a spinning form of dizziness (vertigo), hearing loss and ringing in the ear (tinnitus), and can be disabiling (1). The disease is most common between 40 and 60 years of age, although younger people can also be affected. The incidence is estimated to be between 50 and 350 per hundred thousand per year (2).

It has been suggested that betahistine hydrochloride reduces the frequency and severity of vertiginous episodes and tinnitus and arrests the progression of hearing loss in patients with Ménière's syndrome (1, 3-5).

Betahistine dihydrochloride relaxes the precapillary sphincters and thus improves the microcirculation in the inner ear. This effect occurs both in cramped and normal blood vessels (6-8).

The antivertigo action of betahistine could also be explained as the result of an inhibition of massive impulses to the polysynaptic neurons of the lateral vestibular nucleus (9).

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The usual daily dosage range is 24 to 48 mg administered orally in divided doses. Dosage can be adjusted to suit individual patient needs. Sometimes improvement could be observed only after a couple of weeks of treatment. (10).

Betahistine dihydrochloride salt is used in tablets. The base form of this drug; betahistine (BH), is a good candidate for transdermal delivery. It has low molecular weight (136,2), short elimination half life (3-5 hours), low daily dosage range (24-48 mg as dihydrochloride salt), frequent dosing regimen (3 times a day) and liquid state. Furthermore the drug is contraindicated in the presence of peptic ulcer (11).

Transdermal patches are flexible pharmaceutical preparations of varying sizes and contain one or more active ingredients (12). They have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation (13).

Transdermal therapeutic systems have the advantage of overcoming first pass metabolism. The drug levels can be maintained in the systemic circulation, within the therapeutic window for prolonged periods of time (14).

Following a single administration of the drug, duration of drug action can be extended and the frequency of dosing is reduced, thus, patient compliance can be improved and it reduces inter and intra-patient variability. Another advantage is that the drug therapy can be ended simply by removing the patch from the skin. Also, in the cases where oral delivery is contraindicated or the drug is poorly absorbed from the gastrointestinal tract, transdermal drug administration can be used alternatively (15-19).

The aim of this study was to develop a betahistine transdermal therapeutic system (TTS) by using Eudragit RL 100 and RS 100, pH independent synthetic polymers. Optimum formulations were chosen according to the DSC results and macroscopic properties (general appearance, homogeneity, flexibility, transparency and color) of the formulations.

MATERIALS AND METHODS

Materials

2- (2- Metilaminoethyl) pyridine (Betahistine) was purchased from Sigma Aldrich (USA). Synthetic and pH independent polymers, Eudragit RL 100 and Eudragit RS 100, were received as a gift from Evonik Röhm Pharma (Germany). Plasticisers; triethyl citrate (TEC) and propylene glycole (PG) was obtained from Sigma Aldrich (USA) and the other plasticisers polyethylene glycol (PEG) 400 was purchased from Merck (Germany) and glycerine from Riedel de Haën (Germany). Solvents; acetone and ethyl alcohol were purchased from Sigma Aldrich (USA). All other chemicals were of analytical grade.

Methods

DSC Studies

Betahistine and the other ingredients; Eudragit RL 100, Eudragit RS 100, TEC, PEG 400, PG and glycerine were evaluated for their excipient-drug compatibility (20). Differential scanning calorimetry (DSC) was used to characterize the thermal behavior and to confirm the compatibility of each ingredient with betahistine in the patch. Approximately 10- 20 mg of pure ingredient samples or of (1:1) (w/w) physical mixture samples were weighed into aluminum pans and hermetically sealed to compare with a blank aluminum pan. DSC thermograms were recorded using the DSC instrument (DSC Q 100 TA Instrument) from -90°C to 280°C at the heating rate of 10 °C/ min under nitrogen atmosphere.

Preparation of Matrix Type Transdermal Therapeutic Systems Containing Betahistine

To prepare the formulations, FDA approved polymers, Eudragit RL 100 and Eudragit RS 100, were chosen as matrix forming polymers which are widely used in controlled release dosage forms (21). Formulations were prepared by using solvent evaporation technique.

Different ratios of these two polymers and as the polymers do not have the elasticity needed, triethyl citrate (TEC), polyethylene glycol (PEG) 400, glycerine or propylene glycol in different amounts were tested as plasticisers. Acetone and ethanol were preferred as solvents and the drug BH was used in different amounts.

Plasticizer and polymer (Eudragit RL 100 and/ or Eudragit RS 100) were dissolved in acetone, then betahistine solution in ethyl alcohol was added and stirred by using a mechanical stirrer (Gerhardt). A glass mould of 3 cm diameter was coated with aluminium foil as impermeable backing layer. The solution prepared was poured into this mould and allowed to dry at room temperature. Acetone and ethyl alcohol were used in the minimum amount enough to solve the polymer. Before formulation studies, preformulations without drug were prepared with the same method and different amounts of plasticisers were tried for the optimization. Plasticisers PEG 400 and TEC were tested between 15-30 % and the others; glycerine and PG were tested between 15-30 % of the total polymer amount. Preformulations without betahistine are shown in Table 1.

Evaluation of the Preformulation Systems

The TTS's prepared without drug were evaluated for their general appearance, transparency, color, softness, homogeneity and flexibility.

Table 1. Preformulation studies with different amounts of excipients.

Formulation Code	Eudragit RL 100 (g)	Eudragit RS 100 (g)	PEG 400 (%)	TEC (%)	Glycerine (%)	PG (%)	Acetone (ml)
F 1	1	-	-	-	-	-	4
F 2	-	1	-	-	-	-	4
F 3	0.5	0.5	-	-	-	-	4
F 4	1	-	15	-	-	-	4
F 5	1	-	20	-	-	-	4
F 6	1	-	25	-	-	-	4
F 7	1	-	30	-	-		4
F 8	-	1	15	-	-	-	4
F 9	-	1	20	-	-	-	4
F 10	-	1	25	-	-	-	4
F 11	-	1	30	-	-	-	4
F 12	0.5	0.5	15	-	-	-	4
F 13	0.5	0.5	20	-	-	-	4
F 14	0.5	0.5	25	-	-	-	4
F 15	0.5	0.5	30	-	-	-	4
F 16	1	-	-	15	-	-	4
F 17	1	-	-	20	-	-	4
F 18	1	-	-	25	-	-	4
F 19	1	-	-	30	-	-	4
F 20	-	1	-	15	-	-	4
F 21	-	1	-	20	-	-	4
F 22	-	1	-	25	-	-	4
F 23	-	1	-	30	-	-	4
F 24	0.5	0.5	-	15	-	-	4
F 25	0.5	0.5	-	20	-	-	4
F 26	0.5	0.5	-	25	-	-	4
F 27	0.5	0.5	-	30	-	-	4
F 28	1	-	-	-	30	-	4
F 29	1	-	-	-	40	-	4
F 30	-	1	-	-	30	-	4
F 31	-	1	-	-	40	-	4
F 32	0.5	0.5	-	-	30	-	4
F 33	0.5	0.5	-	-	40	-	4
F 34	1	-	-	-	-	30	4
F 35	1	-	-	-	-	40	4
F 36	-	1	-	-	-	30	4
F 37	-	1	-	-	-	40	4
F 38	0.5	0.5	-	-	-	30	4
F 39	0.5	0.5	-	-	-	40	4

RESULTS AND DISCUSSION

DSC Studies

All the ingredients were tested and no incompatibility was found between the drug and the excipients according to the DSC thermograms shown in Figure 1-7.

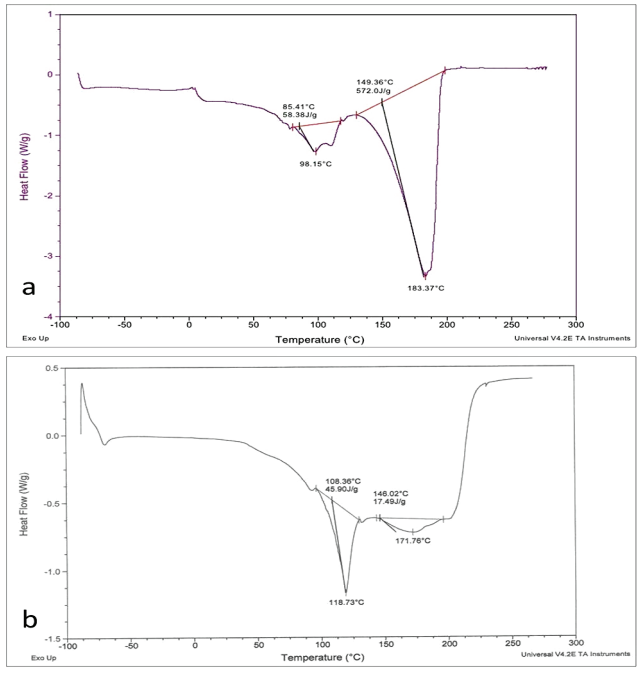

Figure 1. a) DSC thermogram of Glycerine, b) DSC thermogram of BH: Glycerine (1:1) (w/w) physical mixture

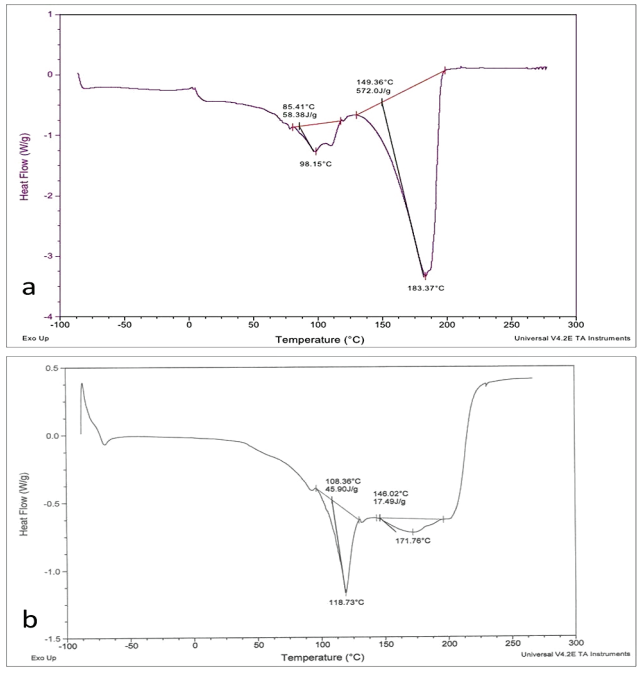

Figure 2. a) DSC thermogram of PG, b) DSC thermogram of BH: PG (1:1) (w/w) physical mixture

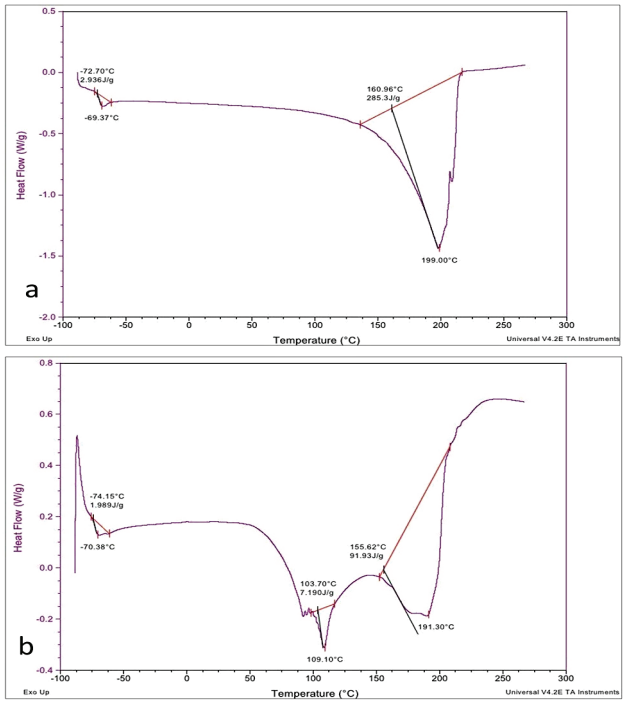

Figure 3. a)DSC thermogram of TEC, b)DSC thermogram of BH:TEC (1:1) (w/w) physical mixture

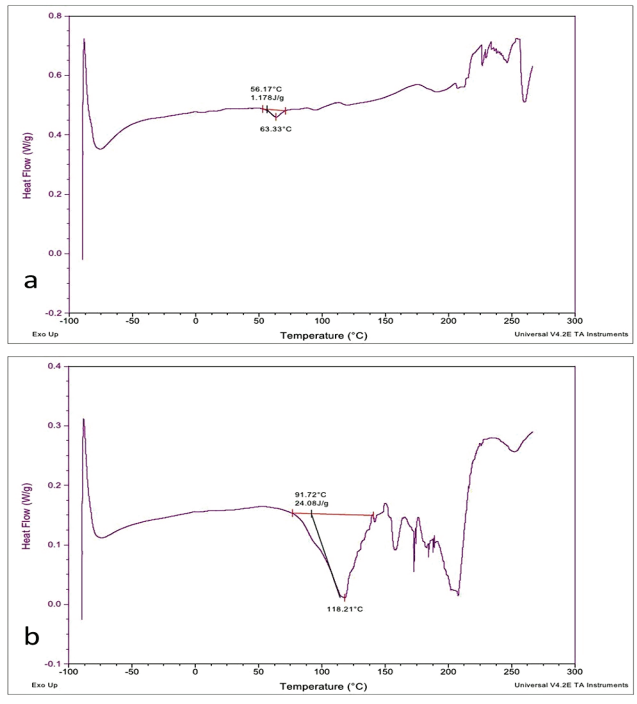

Figure 5.a) DSC thermogram of Eudragit RL 100, b) DSC thermogram of BH: Eudragit RL 100 (1:1) (w/w) physical mixture

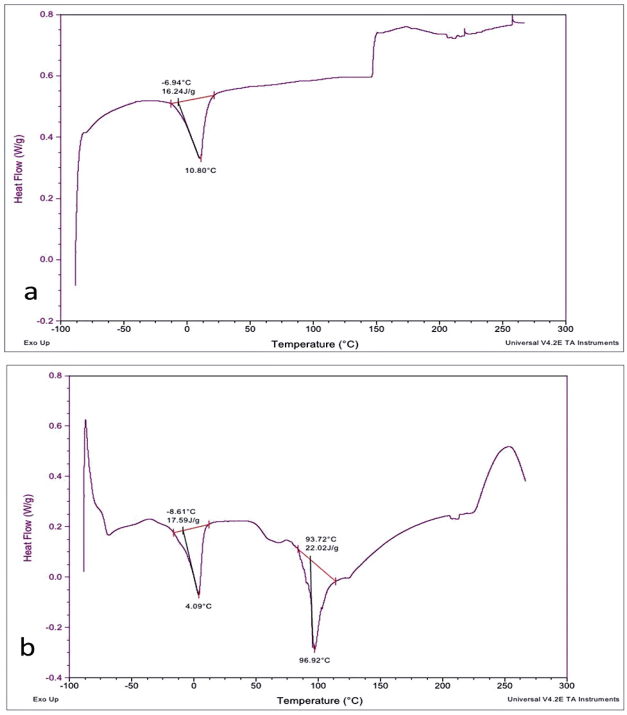

Figure 4.a) DSC thermogram of PEG 400, b) DSC thermogram of BH: PEG 400 (1:1) (w/w) physical mixture

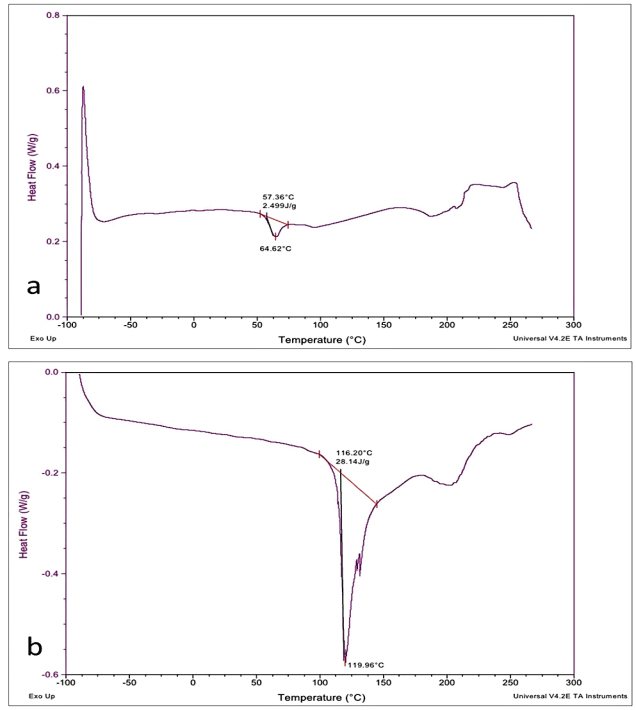

Figure 6.a) DSC thermogram of Eudragit RS 100, b) DSC thermogram of BH: Eudragit RS 100 (1:1) (w/w) physical mixture

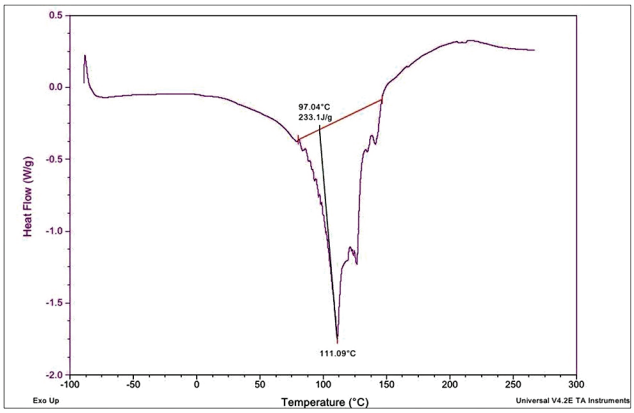

Figure 7. DSC thermogram of BH

Evaluation of the Preformulation Systems

The formulations prepared were evaluated for their macroscopic properties : general appearance, transparency, color, softness, homogeneity and flexibility. Results of all these parameters were examined and optimal ratios were determined. Also adhesive properties were seen to be influenced by increasing the plasticiser concentration especially observed in the formulations prepared with TEC (22). As a result, plasticisers PEG 400 and TEC were decided to be used in 25% of the polymer amount. Glycerine and propylene glycole were decided to be used with PEG 400 or TEC, not to be used separately as a plasticiser.

CONCLUSION

Betahistine and excipients were tested using DSC studies individually and as 1:1 (w/w) drug: excipient physical mixtures. Thermograms were evaluated and no incompatibility was detected.

After DSC studies, preformulation studies were carried out with these polymers and plasticisers. Plasticisers were used in different concentrations together and separately. The formulations prepared were evaluated for their general appearance, transparency, color, softness, homogeneity and flexibility. Optimal plasticiser amounts and formulations were chosen (23) and formulations were chosen to be prepared with BH for further in-vitro and in-vivo studies.

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Betahistin içeren transdermal terapötik sistemlerin önformülasyon çalışmaları

ÖZET

Ménière hastalığı gibi periferal dolaşım bozukluklarının eşlik ettiği hastalıklarda, baş dönmesi ve kulak çınlaması gibi durumların sıklığını azaltmada betahistin kullanılmaktadır. İlacın yarı ömrü kısadır ve hızlı eliminasyona bağlı olarak günde üç defa alınması gerekir. Peptik ülser öyküsü olan hastalarda ilacın kontrendike olması ve sık alma zorluğu gibi nedenler oral yol dışında başka bir yol arayışını gerektirmektedir. Bu çalışmanın amacı FDA onaylı sentetik polimerler olan Eudragit RL 100 ve Eudragit RS 100 ile betahistin içeren transdermal terapötik sistem formülasyonları hazırlamaktır. İçerikteki bileşenlerin tamamı Diferansiyel Taramalı Kalorimetre (DSC) testleri kullanılarak yardımcı madde-ilaç geçimliliği açısından değerlendirilmiştir. Farklı yardımcı madde oranlarıyla formülasyonlar hazırlanmış ve makroskobik özellikleri açısından (genel görünüm, homojenite, esneklik, şeffaflık ve renk) değerlendirilmiştir. İlaç ve yardımcı maddeler arasında herhangi bir geçimsizlik olmadığı sonucuna varılmıştır. Formülasyonların makroskobik özelliklerine dayanarak yardımcı madde oranları optimize edilmiştir.

Anahtar sözcükler: Betahistin, transdermal terapötik sistem, DSC, Eudragit

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