

Studies on the development of rapidly disintegrating hyoscine butylbromide tablets

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ABSTRACT: The objective of this study was to prepare hyoscine butylbromide (a drug with bitter taste) tablets that can rapidly disintegrate in saliva. The granules were prepared by the extrusion method using aminoalkyl methacrylate copolymers (Eudragit E-100). The drugs dissolved rapidly in medium at pH 1.2 in a dissolution test while none of the drugs dissolved from the granules (% of dissolved < 5%) even after 8 h at pH 6.8. Rapidly disintegrating tablets were prepared using prepared taste-masked granules and a mixture of excipients consisting of crystalline cellulose (Avicel PH-102) and low-substituted hydroxypropylcellulose (L-HPC, LH-11). The granules and excipients were mixed well (mixing ratio by weight, crystalline cellulose: L-HPC, was 8:2) with 1% magnesium stearate as a lubricant and subsequently compressed at 500-1,500 kgf in a single-punch tableting machine. The prepared tablets (compressed at 500 kgf) containing the taste-masked granules have significant strength (crushing strength was 3.5 kg), and a rapid disintegration time (within 30 sec) was observed in the saliva of healthy volunteers. None of the volunteers sensed any bitter taste after the disintegration of the tablet that contained the taste-masked granules. The results confirmed that rapidly disintegrating tablets can be prepared using these taste-masked granules and excipients that are commonly used in tablet preparation.

Key Words: Hyuocine butylbromide, fast disintegrant tablets, Eudragit E-100, tast masking

Introduction

Pharmaceutical preparations for the elderly have recently been developed to improve their treatment

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compliance and quality of life (QOL) (1). Fast-disintegrating tablets have been in ever-increasing demand since the last decade, and the field has become a rapidly growing area in the pharmaceutical industry (2-6). The preparation of rapidly disintegrating tablets consists of crystalline cellulose (Avicel PH 102) and low-substituted hydroxypropylcellulose (L-HPC), which are commonly used in the manufacture of conventional tablets. The rapidly disintegrating tablet can be prepared by direct compression at a low compression force, 100-300 kgf (7,8). The tablets prepared disintegrated rapidly in saliva and a small amount of water, and the disintegration was complete within 30 sec. Other excipients used in the preparation of rapidly disintegrated tablets include amorphous sucrose (9), glycine, and carboxymethylcellulose (10). High-porosity compressed drug tablets that are soluble in saliva have successfully been prepared using mannitol, a water-soluble excipient (11). A tablet prepared by the compression method using only mannitol had a long dissolution time (> 120 sec). However, highly porous tablets could be prepared by subliming camphor after compressing the mixture of the drug and mannitol and camphor particles. High-porosity tablets thus prepared completely dissolved in saliva within 20 sec (11). The prepared tablets contained meclizine (HCl salt, powder), an antiemetic and antivertigo agent as the active component, and can be taken for motion sickness even when water is not available (12). Thus tablet preparation is highly useful for the treatment of kinetosis. With rapidly disintegrating tablets, there is a problem of the drug's bitter taste due to the dissolution of the active component in the mouth. Taste masking must be investigated prior to preparing rapidly disintegrating tablets of drugs with a bitter taste. In the present study, hyoscine butylbromide, which is extremely bitter, was chosen as the model drug and prepared as rapidly disintegrating tablets using taste-masked granules such as the aminoalkyl methacrylate copolymers. Hyoscine butylbromide has an antimuscarinic effect and is used as an antispasmodic agent (13).

Materials and Methods

Materials

Hyoscine butylbromide, crystalline cellulose (Avicel PH-102), low-substituted hydroxypropylcellulose (L-HPC, LH-110), and magnesium stearate were kindly supplied by the EIPICO Pharmaceutical Company, Egypt. Aminoalkyl methacrylate copolymers (Eudragit E-100) were supplied by Rohm GmbH (Germany). Ethanol ($\geq 99\%$) and all other reagents used were of analytical grade.

Preparation of granules and rapidly disintegrating tablets

The composition of each tablet tested is listed in Table 1. The drug hyoscine butylbromide (HBB) was mixed with powdered Eudragit E-100 in a drum mixture, and then 10% ethanol was added to the mixture of the drug and Eudragit in a glass beaker. Then, a gel containing the mixture of the drug and Eudragit E-100 was prepared; using this prepared gel, taste-masked granules were prepared by the extrusion method. The prepared gel was manually extended (pressed out) using a syringe. After extrusion of the gel, ethanol was removed by evaporation overnight and subsequently the solidified gel in the shape of a string was crushed into granules using a mortar. An Erweka single-punch tableting machine was used to prepare tablets with an 8-mm diameter using a compression force of 500-1500 Kp for a target weight of 180 mg. The taste-masked tablets were prepared using a mixture of the taste-masked granules, excipient mixture, crystalline cellulose and L-HPC at mixing ratios by weight of crystalline cellulose of L-HPC = 8:2, and magnesium stearate (1%). Additionally, tablets were prepared using a powdered mixture of the drug and Eudragit E-100 (without granulation) and magnesium stearate (1%) as a control tablet.

Evaluation of the tablets prepared

The crushing strength of the tablets in response to diametrical compression force was measured with a digital crushing strength measuring machine (Pharma Test hardness tester).

The *in vitro* disintegration time was measured for 6 tablets; one tablet was placed in each tube of the basket, which was then immersed in water ($37 \pm 2^\circ\text{C}$). The time required for complete disintegration of the tablet in each tube of the basket was recorded in seconds.

The *in vitro* dissolution test was conducted using a USP II dissolution apparatus. The materials (tablet contents and masked granules) were dried overnight in a desiccator to remove excess moisture and subjected to a dissolution test in a machine equipped with an autosampling apparatus (HP, Japan). The USP II dissolution test basket was attached to a spindle and

Table 1. Composition of the Tablets

Materials	Amount/mg
Hyoscine butylbromide	5
Eudragit E-100	50-75
Crystalline cellulose	78-103
L-HPC	20
Magnesium stearate	2
Total	180

placed in a dissolution bath containing 900 mL of USP II 1st fluid (pH 1.2) and the 2nd fluid (pH 6.8) for the disintegration test or citric acid-NaOH buffer solution (pH 5.0) (14) and maintained at $37 \pm 0.5^\circ\text{C}$. The spindle was rotated at 100 rpm, and the samples were withdrawn and analyzed by UV spectrometry at 211 nm.

For determination of the *in vivo* disintegration time, ten healthy volunteers, from whom informed consent was first obtained, randomly took one tablet and the time required for complete disintegration of the tablet in the mouth, without biting and without drinking water, was measured (15). The sensory test for a bitter taste as described by Kimura *et al.* (16) was used with slight modification. Briefly, the same ten volunteers mentioned in the determination of the disintegration time in saliva held the disintegrated materials in their mouths for 30 sec. Immediately after the *in vivo* disintegration test, volunteers rinsed their mouths out without ingesting the disintegrated particles.

Results and Discussion

Dissolution profiles of hyoscine butylbromide from the taste-masked granules prepared from the aminoalkyl methacrylate copolymer

Aminoalkyl Methacrylate Copolymer (Eudragit E-100) dissolved in an acidic pH (low pH region) but not in the neutral pH region. Therefore, Eudragit E-100 was used as an acid-soluble (gastric soluble) coating material for the compound. In the preliminary study, the taste-masked granule using Eudragit E-100 was prepared at various mixing ratios by weight. Although the mixing ratio of the active component and Eudragit E-100 was set arbitrarily, the ratio was ultimately selected to be HBB: Eudragit E-100 = 1:10 (Table 1). Figure 1 shows the dissolution profiles of the drugs from the prepared granules. The prepared granules dissolved slightly in the fluid (pH 6.8) and maintained their granule shape. Consequently, none of the drugs dissolved from the granules (% of dissolved, $< 5\%$) even at 480 min after the beginning of the dissolution test. On the other hand, the dissolution of the drug was rapid at a pH of 1.2. The drug dissolution was complete at 15 min after the beginning of the test. When the pH in the stomach is increased (low gastric acidity) by drug or foods and in patients with greater stomach acidity, dissolution of the

drug from the taste-masked granules should decrease. Therefore, dissolution of HBB from taste-masked granules was tested in a buffer solution at pH 5.0. Consequently, a similar profile of rapid dissolution was obtained at pH 5.0 (Figure 1).

The results of the dissolution test imply that HBB does not dissolve from the prepared granules in saliva with a pH in the neutral region, but they rapidly dissolve in gastric juices where the pH is acidic. As shown in Table 2, the volunteers who took the prepared granules did not sense the bitter taste of the drug. Therefore, taste-masked granules can be prepared using Eudragit E-100.

Evaluation of the rapidly disintegrating tablets prepared using the taste-masked granules and excipients of crystalline cellulose and L-HPC

The HBB content in tablets was chosen to be equal to the dose. Crystalline and L-HPC were used as the excipients for the rapidly disintegrating tablets (16).

Figure 2 shows the relationship between the compression force on the mixture of the taste-masked granules and excipients and the crushing strength of the prepared tablet. The crushing strength was about 2 kg for the tablet compressed at 500 kgf while it exceeded 6 kg for tablets compressed at 1,500 kgf. Compressibility

Table 2. Disintegration time in mouth and sensory test for the tablets contains taste-masked granules

Volunteer number	Hyuocine butylbromide	
	Masked tablets	Control tablets
1	27 (-)	22 (+)
2	23 (-)	26 (+)
3	25 (-)	23 (+)
4	28 (-)	23 (+)
5	29 (-)	24 (+)
6	26 (-)	22 (+)
7	25 (-)	25 (+)
8	24 (-)	22 (+)
9	27 (-)	20 (+)
10	28 (-)	24 (+)
Mean	26	23.1
+ SD	1.93	1.73

Bitter taste: (-) no, (+) yes

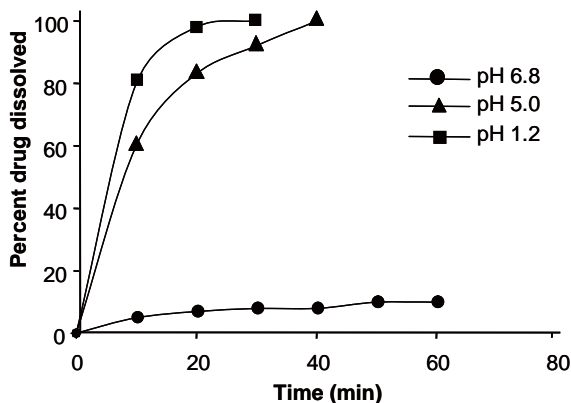


Figure 1. Percent of drug released from the taste-masked granules prepared with Eudragit E-100.

decreased when the content of Eudragit E-100 increased in comparison to those of other excipients (crystalline cellulose and L-HPC). Consequently, the crushing strength of the prepared tablets was lower than that of controlled tablets.

Figure 3 illustrates the relationship between the compression force and the *in vitro* disintegration time of the prepared tablet. When the compression force was

Table 3. Percent of drug released from the granules prepared with Eudragit E-100

Time (sec)	pH		
	1.2	5.0	6.8
10	80	60	5
20	98	83	7
30	100	92	8
40		100	8
50			10
60			10

Table 4. Relationship between crushing strength and *in vivo* disintegration time of the tablets

Compression Force	Crushing Strength	<i>In vivo</i> disintegration time
500	2.1	7.5
1000	2.4	12
1500	6.0	26

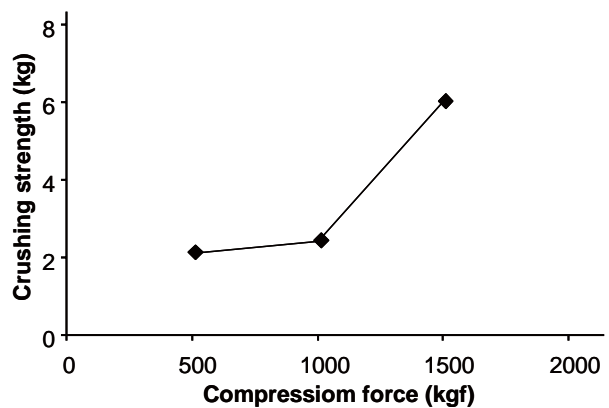


Figure 2. Relationship between compression force and crushing strength of the tablets.

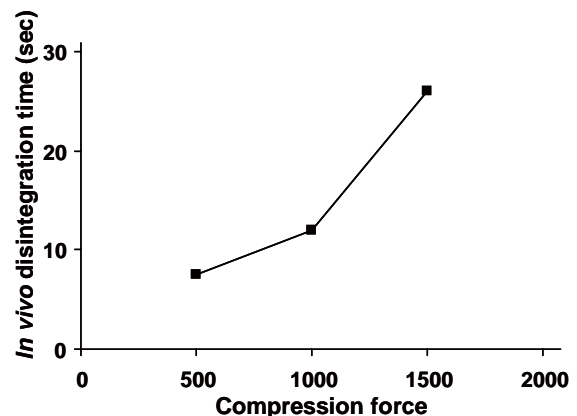


Figure 3. Relationship between compression force and *in vivo* disintegration time of the tablets.

increased, the crushing strength increased markedly and the *in vitro* disintegration time was also prolonged. To date, the best criteria for the disintegration time of rapidly disintegrating tablets have yet to be confirmed. This study sought to achieve a maximum disintegration time of 30 sec. With the tablets in the study, rapid disintegration of the prepared tablets can be achieved by using a mixture of the taste-masked granules and excipients at various compounding ratios when the compression force is adjusted to below 1,000 kgf. The disintegration times of HBB tablets were found to be under 20 sec *in vitro* when the compression force was 500 kgf. To examine the disintegration of the prepared tablet in the mouth, the *in vitro* disintegration time was measured by the method described in Materials and methods. As the same time, a sensory test was performed beforehand to evaluate the degree of taste masking. For the control tablet, the drug, and excipients without granulation, the mixture of the active component, crystalline cellulose, L-HPC and Eudragit E-100 were compressed at the same force as for tablets containing the taste-masked granules. The results are summarized in Table 2. In the mouth, the disintegration time of HBB tablets containing the taste-masked granules prepared using a compression force of 500 kgf was approximately 20 sec. Fortunately, none of the volunteers sensed any bitter taste after disintegration of the tablets containing the taste-masked granules, but they strongly sensed the bitter taste when the control tablet disintegrated in their mouths. The results of the sensory test suggest that formulation of Eudragit E-100 matrices (granules) plays an essential role in the screening of the bitter taste. Although dissolution in the stomach was not examined in the volunteers, rapid dissolution would appear to occur in the gastric juices. Concerning the mechanisms of rapid disintegration by the excipients of crystalline cellulose and L-HPC, a higher level of porosity for compressed tablets using crystalline cellulose and L-HPC would appear to be preferable for disintegration in a small amount of water. Bi *et al.* suggested that the disintegration of crystalline cellulose L-HPC tablet is affected mainly by tablet porosity, hydrophilicity, swelling ability, and interparticle force (16).

Conclusion

Rapidly disintegrating tablets were prepared using taste-masking granules and excipients that are commonly used in tablet preparation. The method of preparation is useful for the preparation of rapidly disintegrating tablets containing a bitter-tasting drug like hyoscine butylbromide.

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