A Novel Approach to Formulate and Optimize Orally Disintegrating Tablets of Bambuterol Hydrochloride

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Abstract

The aim of this article was to choose the optimal ingredients for oral disintegrating tablets of bambuterol hydrochloride (BBH) and use a novel approach to measure disintegration time. The disintegration time measured by a new approach was compared with disintegration time measured in oral cavity and conventional disintegration test. The result shows that the new apparatus is suitable for measuring the disintegration time. The effect of ingredients (diluents, disintegrants and adhesives) on the characteristics of the tablets was investigated. The orally disintegrating tablets of BBH were prepared by wet granulation. The results showed that the optimum proportion was 10 mg BBH, 100 mg lactose, 80 mg MCC, 10 mg crospovidone (PVPP), 2 mg aspartame, 2 mg DL-malic acid. The orally disintegrating tablet disintegrated rapidly, tasted good and could be taken convenient.

Keywords: Orally disintegrating tablets (ODts); Bambuterol hydrochloride; Disintegration Time (DT); A New Apparatus; Formulation

Introduction

Because of lifestyle changes, a demand has arisen for the development of pharmaceutical forms that can be readily handled and taken by many patients. Rapidly disintegrating or dissolving drug delivery systems, in which drugs are administrated orally for direct ingestion without water, are particularly useful for geriatric, pediatric and traveling patients. These new forms of medicine are quite advantageous because they can be taken without any chewing or prior dispersion and/or dissolution processes [1-3]. Some of them (sublingual or buccal tablets) display a spontaneous disaggregation and fast absorption in the mouth upon contact with saliva [4]. Therefore, numerous studies on various compositions and manufacturing methods of orally disintegrating or dissolving tablets (ODTs) have been performed [5,6].

DT is an important coefficient to orally disintegrating tablets. Compared with common tablet, ODTs disintegrate more quickly and need less solution. So the method to measure the common tablet disintegration time is not suitable for ODTs. At present, the USP, the EP and the CP are not established orally disintegrating tablet disintegration time method. Scholars have done many researches such as a modified dissolution test, fluid water [7] or a CCD camera [8] to obtain the scientific and reasonable method to measure DT. However, the proposed tests so far lack universality and convenience.

Bambuterol hydrochloride (BBH) is a direct acting sympathomimetic with predominantly-adrenergic activity (β2-agonist) [9]. It is an ester prodrug of β2 adrenergic agonist terbutaline [10]. The dosage form of BBH is available in the market for prophylaxis and treatment of chronic asthma and chronic bronchitis in pediatrics.

In this study we want to choose the optimal ingredients for oral disintegrating tablets of bambuterol hydrochloride (BBH) and use a novel approach to measure disintegration time.

Experimental Materials

BBH was obtained from Jiu Dian Pharmaceutical Co. Ltd (Hunan, People’s Republic of China). MCC, PVP K30, PVPP were obtained from Shan He Excipients Co. Ltd (Anhui, People’s Republic of China). Lactose was obtained from Kang Fu Biological Engineering Co. Ltd (Zhenjiang, People’s Republic of China). Mannitol was obtained from Hua Xu Pharmaceutical Co. Ltd (Hebei, People’s Republic of China). Magnesium stearate was obtained from Ao Da Pharmaceutical Co. Ltd (Liaoning, People’s Republic of China). All reagents were of analytical grade and used as received.

Preparation of Tablets

Tablets were manufactured by wet granulation (Figure 1). First, the BBH and the various quickly disintegrating tablet adjuvants (diluent, disintegrating agent and lubricant) were screened to produce a homogeneous mixture. The resulting mixtures were passed through a 100-mesh sieve and then granulated in a mortar using binder. The obtained granulates were dried in a 60°C oven (101-2A,Tianjin Taisite Instrument Co. Ltd, People’s Republic of China) for 1 hour.

Figure 1: Apparatus of proposed new disintegration method for the vitro disintegration time determination.
Results and Discussion

Effect of diluent on disintegrating time

Lactose, sucrose, mannitol and starch are used as diluents in ODTs. After reviewing some papers, we decided to use lactose, glucose, mannitol and sucrose as diluents in experiments. F1, F2, F3, F4 in table 1 shows that lactose is the best choice, for F1 disintegrates in 53s. F1 could be perfect compressed into tablets, and didn’t have collapse phenomenon.

Effect of disintegrating agent on disintegrating time

Disintegrating agent is the key factor to influence DT. We always use CMS-Na, MCC, L-HPC and PVP as disintegrating agent. Because MCC has porous structure and strong capillary effect, water can penetrate tablets and make it disintegrated. Due to its weak swelling property, it is often used with other disintegrating agents. Combination of MCC with PVP was employed in this experiment using F1, F5, F6, F7 (MCC worked as variable, and PVP remained the same amount) and F1, F8, F9, F10 (PVP worked as variable, and MCC remained the same amount). Table 1 shows that DT is shorter, when we increase amount of MCC and PVP. Because MCC tastes bad, and PVP is expensive, we use F1 to reduce cost and ensure DT.

Effect of the method of addition PVP on disintegrating time

In general, addition PVP from inside and outside can shorten DT. To verify it, we design experiments using F1, F11, F12. From table 1 we can see that F11 has shorter DT than F1 and F12. So addition PVP from inside and outside shortens DT.

Effect of moistening agent to DT and granulation

Moistening agent has an influence on granulation and DT, so it is necessary to screen a suitable moistening agent. We used distilled water, ethanol, 70% ethanol and 10% PVP ethanol solution as moistening agent. The result is listed in table 2.

Table 2 shows that ethanol is the best choice for moistening agent. We used distilled water, ethanol, 70% ethanol and 10% PVP ethanol solution as moistening agent. The result is listed in table 2.

Effect of taste masking on taste

BBH needs to dissolve in orally, so the taste is important. BBH

| Component | BBH (mg) | MCC (mg) | PVPP (mg) | Lactose (mg) | Hydrated mannitol (mg) | Mannitol (mg) | Correctives (mg) | DT in the new apparatus (s) | DT in disintegration apparatus (s) | DT in oral cavity (s) |
|-----------|---------|---------|-----------|-------------|-----------------------|--------------|----------------|--------------------------|---------------------------------|------------------------|
| F1        | 10      | 80      | 10        | 100         | 0                     | 0            | 10             | 53 ± 2                   | 13 ± 1                           | 62 ± 8                  |
| F2        | 10      | 80      | 10        | 0           | 100                   | 0            | 0              | 90 ± 3                   | 24 ± 2                           | 110 ± 10                |
| F3        | 10      | 180     | 10        | 0           | 0                     | 100          | 10             | >120                     | 38 ± 3                           | >120                   |
| F4        | 10      | 80      | 10        | 0           | 0                     | 100          | 10             | 70 ± 3                   | 12 ± 2                           | 83 ± 9                  |
| F5        | 10      | 0       | 10        | 180         | 10                    | 0            | 10             | >120                     | 40 ± 3                           | >120                   |
| F6        | 10      | 60      | 10        | 120         | 10                    | 0            | 10             | 65 ± 3                   | 28 ± 2                           | 82 ± 9                  |
| F7        | 10      | 100     | 10        | 80          | 10                    | 100          | 10             | 50 ± 2                   | 10 ± 1                           | 62 ± 8                  |
| F8        | 10      | 80      | 8         | 102         | 10                    | 65 ± 3       | 10             | >120                     | 37 ± 2                           | >120                   |
| F9        | 10      | 80      | 0         | 110         | 10                    | >120         | 10             | 45 ± 2                   | 14 ± 2                           | 60 ± 9                  |
| F10       | 10      | 80      | 12        | 98          | 10                    | 48 ± 2       | 10             | >120                     | 43 ± 4                           | >120                   |

Table 1: The formulations of orally disintegrating tablets of BBH.
itself is bitter. That is why we need taste masking to improve the taste. According to the test result, BBH ODTs with aspartame and DL-malic acid can effectively improve the taste. And ten healthy volunteers feel no bitterness when they get BBH ODTs in their mouth.

**Effect of hardness on DT**

Tablet properties such as hardness are closely linked to causing DT. The preferable strength of the ODT is about 40 N and more preferably between 30 and 80 N. Ten tablets from each of F1, F10, F11 were investigated in this test, for these formulations have good DT. The hardness of these tablets shows in table 3. From the results we can see that all these three formulations complied with regulation. When we take DT into account, F11 is the best choice.

**Friability test**

Tablet friability is a measurement of the tablet’s physical strength. It was stated that an acceptable friability for tablets not exceeding 1%. In friability test, we measured F1, F10, F11, for these formulation’s DT are short. The results of friability test shown in table 4. From table 4 we can see that F1, F10, F11 complied with the regulation as none of them had percentage loss in tablets’ weights that exceeded 1%, no tablets was cracked, split or broken in either formulation. Because F11 has shorter DT, it is the best choice.

**Evaluate of the novel method to measure DT**

The DT in the human sensory test is varied from table 1. From table 1, we can see that good correlation was obtained between the DT determined in oral cavity and the new apparatus. The conventional disintegration test uses disintegration apparatus to determine ODTs’ DT, however it is doubtful whether it is suitable, for it requires a lot of water and shakes violently upper and lower. That makes ODTs disintegrate too fast to compare DT of different formulations. And we can see that DT determined by the conventional method does not have good correlation with DT determined in oral cavity. So a suitable disintegration test is needed. A critical factor might be the amount of water used in the test method, for the saliva volume is very small. The method we proposed utilizes only 4 ml water to penetration of water. Another factor is mechanical vibration intensity of apparatus. The apparatus we used stir at 50 r/min, so it shakes less intense than the disintegration test uses disintegration apparatus to determine ODTs’ DT, however it is doubtful whether it is suitable, for it requires a lot of water and shakes violently upper and lower. That makes ODTs disintegrate too fast to compare DT of different formulations. And we can see that DT determined by the conventional method does not have good correlation with DT determined in oral cavity. So a suitable disintegration test is needed. A critical factor might be the amount of water used in the test method, for the saliva volume is very small. The method we proposed utilizes only 4 ml water to penetration of water. Another factor is mechanical vibration intensity of apparatus. The apparatus we used stir at 50 r/min, so it shakes less intense than disintegration apparatus. From this point of view, our method also presents a clear advantage.

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**Table 2:** Effect of moistening agent on DT and granulation.

| moistening agent | granulation | DT (s) |
|------------------|-------------|--------|
| distilled water (F11) | bad | - |
| Ethanol (F11) | very good | 48 |
| 70%ethanol (F11) | bad | - |
| 10%PVP ethanol (F11) | very good | >120 |

**Table 3:** The hardness of F1, F10, F11.

| Formulation | F1 (N) | F10 (N) | F11 (N) |
|-------------|--------|---------|---------|
| No.1 | 41 | 40 | 40 |
| No.2 | 40 | 41 | 40 |
| No.3 | 42 | 42 | 41 |
| No.4 | 41 | 41 | 42 |
| No.5 | 42 | 40 | 42 |
| No.6 | 41 | 42 | 41 |
| No.7 | 40 | 41 | 40 |
| No.8 | 41 | 41 | 41 |
| No.9 | 42 | 41 | 42 |
| No.10 | 41 | 40 | 41 |

**Table 4:** Friability test of F1, F10, F11.

| Formulation | F1 | F10 | F11 |
|-------------|----|-----|-----|
| weight before measured (g) | 6.012 | 6.008 | 5.997 |
| weight after measured (g) | 5.994 | 5.978 | 5.961 |
| lose weight (g) | 0.018 | 0.030 | 0.036 |
| lose weight% | 0.3% | 0.5% | 0.6% |
| number of tablets with cracked, split or broken | 0 | 0 | 0 |