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Research paper

Quality by Design (QbD) approach to optimize the formulation of a bilayer combination tablet (Telmiduo®) manufactured via high shear wet granulation

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ABSTRACT

A bilayer tablet, which consisted of telmisartan and amlodipine besylate, was formulated based on a Quality by Design (QbD) approach. The control and response factors were determined based on primary knowledge and the target values of the control tablet (Twynsta®). A D-optimal mixture design was used to obtain the optimal formulations in terms of D-mannitol, crospovidone, and MCC for the telmisartan layer, and CCM-Na, PVP K25, and Prosolv for the amlodipine layer. The quantitative effects of the different formulation factors on the response factors were accurately predicted using the equations of best fit and a strong linearity was observed between the predicted and actual values of the response factors. The optimized bilayer tablet was obtained using a numeric optimization technique and was characterized compared with a control (Twynsta®) by using various physical evaluations and *in vivo* pharmacokinetic parameters. The physical stability of Telmiduo® was greater than that of Twynsta® owing to the improvement of formulation factors. The *in vivo* pharmacokinetic parameters suggested that Telmiduo® might have pharmaceutical equivalence and bioequivalence with Twynsta®. Therefore, the bilayer tablet that consisted of telmisartan and amlodipine besylate could be produced using a more economical and simpler method than that used to produce Twynsta®. Moreover, the suitability of QbD for effective product development in the pharmaceutical industry was shown.

1. Introduction

Quality by Design (QbD) is an efficient, systematic, risk-controlled, and knowledge-based method, which focuses on the use of extensive preliminary design in order to improve the quality of pharmaceutical products (Yu, 2008). The QbD method can be performed on the entire pharmaceutical production process, or certain parts, and also in the early research and development stages (Charoo and Ali, 2013; Charoo et al., 2012; Huang et al., 2009; Tomba et al., 2013; Westermarck et al., 1999; Zidan et al., 2007). The QbD method can help generate a time-efficient and cost-effective process, narrow the gap between science and industry, and facilitate the innovation transfer process of the introduction of new drugs to market (Chatterjee, 2011; Westermarck et al., 1999). The strategy for QbD-based development in pharmaceutical technology adheres to the following process: a) the definition of a QTPP (Quality Target Product Profile); b) the identification of CQAs (Critical Quality Attributes) and CPPs (Critical Process Parameters); and c) the initial RA (Risk Assessment) and RAs after development. The QTPP contains the therapeutic requirements and other quality demands, including the dissolution profile and stability aspects (Wu et al., 2009). A CQA can be defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." Raw materials (e.g., drug substances or excipients), intermediates (e.g., in-process materials), and final drug products represent CQAs of pharmaceutical preparations (Rathore and Winkle, 2009; Westermarck et al., 1999). The CPP is any measurable input (e.g., input material attribute or operating parameter) or output (e.g., process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. A key purpose of RAs in pharmaceutical development is to identify which material attributes and process parameters affect the drug product CQAs; that is, to understand and predict the sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs meet the desired requirements.

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Table 1
Experimental design for telmisartan layer and amlodipine layer.

Run order	Telmisartan layer								
	Fixed factors						Control factors		
	Telmisartan (mg)	NaOH (mg)	Meglumine (mg)	PVP K25 (mg)	F-Melt (mg)	$CaHPO_4$ (mg)	D-Mannitol (mg)	Crospovidone (mg)	MCC (mg)
							x_1	x_2	x_3
1	80	6.7	24	12	20	9.3	196.00	118.00	9.00
2	80	6.7	24	12	20	9.3	153.88	113.40	55.72
3	80	6.7	24	12	20	9.3	165.02	120.71	37.26
4	80	6.7	24	12	20	9.3	178.43	104.17	40.40
5	80	6.7	24	12	20	9.3	165.02	120.71	37.26
6	80	6.7	24	12	20	9.3	165.02	120.71	37.26
7	80	6.7	24	12	20	9.3	136.00	118.00	69.00
8	80	6.7	24	12	20	9.3	136.00	148.00	39.00
9	80	6.7	24	12	20	9.3	166.00	148.00	9.00
10	80	6.7	24	12	20	9.3	176.65	129.11	17.24
11	80	6.7	24	12	20	9.3	157.91	96.09	69.00
12	80	6.7	24	12	20	9.3	181.75	88.00	53.25
13	80	6.7	24	12	20	9.3	196.00	101.50	25.50
14	80	6.7	24	12	20	9.3	166.00	148.00	9.00
15	80	6.7	24	12	20	9.3	181.75	88.00	53.25
16	80	6.7	24	12	20	9.3	136.00	148.00	39.00

Run order	Amlodipine layer				
	Fixed factors		Control factors		
	Amlodipine besylate (mg)	St-mg (mg)	CCM-Na (mg) a_1	PVP K25 (mg) a_2	1 Prosolv (mg) a_3
1	6.94	1.5	8.17	0.00	83.40
2	6.94	1.5	7.19	4.69	79.69
3	6.94	1.5	7.19	4.69	79.69
4	6.94	1.5	0.00	5.90	85.66
5	6.94	1.5	7.19	4.69	79.69
6	6.94	1.5	1.57	0.00	90.00
7	6.94	1.5	11.57	10.00	70.00
8	6.94	1.5	7.19	4.69	79.69
9	6.94	1.5	3.86	1.82	85.89
10	6.94	1.5	0.00	1.57	90.00
11	6.94	1.5	7.19	4.69	79.69
12	6.94	1.5	0.00	10.00	81.57
13	6.94	1.5	8.17	0.00	83.40
14	6.94	1.5	1.57	0.00	90.00
15	6.94	1.5	15.00	0.00	76.57
16	6.94	1.5	3.68	5.37	82.52
17	6.94	1.5	11.57	10.00	70.00
18	6.94	1.5	3.49	8.60	79.48
19	6.94	1.5	0.00	10.00	81.57
20	6.94	1.5	15.00	6.57	70.00
21	6.94	1.5	10.68	5.96	74.93
22	6.94	1.5	15.00	0.00	76.57
23	6.94	1.5	5.82	10.00	75.75
24	6.94	1.5	7.19	4.69	79.69
25	6.94	1.5	11.04	1.40	79.13

Recently, combination drug therapies have become one of the most frequently used dosage forms, as they present a promising strategy for tackling diseases through improvements in efficacy and reduction of side effects (Xu et al., 2017). Telmisartan is an angiotensin receptor blocker, which shows high affinity for the angiotensin II type 1 receptors (Galzerano et al., 2010; Younis et al., 2016). Amlodipine selectively inhibits calcium ion influx in vascular smooth muscle and cardiac muscle, which inhibits the contractile processes of these tissues. The resulting peripheral arterial vasodilation and reduction in peripheral vascular resistance reduces arterial blood pressure (Lurbe et al., 2009; Van Der Vossen et al., 2016). The combination treatment of telmisartan and amlodipine can improve efficacy and reduce side effects (Balraj and Faruqui, 2017). This drug is sold in the market under the trade name of Twynsta® (Boehringer Ingelheim, Ingelheim, Germany).

According to the BCS, telmisartan is a class II drug with a logP value of 7.23 and poor water solubility, whereas it has a high solubility in alkaline solution (Tran et al., 2008). Therefore, alkalizing agents or solubilization agents are required in product manufacturing and a large amount of solvent may be necessary to dissolve these agents. Owing to the application of a large amount of water in manufacturing processes, fluid bed granulation or spray-drying techniques are used to obtain drug particles (Friedl and Schepky, 2009; Park et al., 2011). For the preparation of tablets, these techniques require expensive facilities and involve more steps than the wet granulation technique. Moreover, sorbitol, a major constituent of the tablet, is used as a water soluble diluent of Twynsta® (Park et al., 2011). Twynsta® requires alu/alu blister packaging to prevent humidity invasion as sorbitol can easily