EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 8
852-857
Year: 2017

INVESTIGATION OF FUNCTIONALITY OF NOVEL GRANULATION BINDER-DISINTEGRANT IN FORMULATION OF AMOXICILLIN TRIHYDRATE DISPERSIBLE TABLETS

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Article Received on 23/05/2017 **Article Revised on 13/06/2017** **Article Accepted on 04/07/2017**

ABSTRACT

An excipient is the component other than active ingredient; added to the formulation to perform proposed function. Binders confer structural strength required to the tablets i.e. compactibility and disintegrant is an essential component to provoke disintegration followed by dissolution of tablets. Starch is used as binder and /or disintegrant in tablet formulations but has to be added in high proportion to get its duel functionality. Novel blend of HPMC K100LV and gel obtained from psyllium husk was investigated for its dual functionality as 'granulation binder-disintegrant' in the present work. Granulation binder functionality of novel blend was confirmed by Heckel treatment and mechanism of disintegration was determined by adopting the strategy suggested by Bele and Derle, 2012. Novel blend disintegrated by swelling as well as deformation. Dispersible tablet formulation of amoxicillin trihydrate was developed and prepared by using a novel blend as a 'granulation binder-disintegrant'. A 2^2 factorial design was implemented to study the effect of formulation and processing variables on the performance of dispersible tablet formulation of amoxicillin trihydrate. It was observed that tablets prepared at high compression pressure disintegrated faster; and hardness was also increased as novel 'granulation binder-disintegrant' imparted more compactibility at high pressure.

KEYWORDS: Granulation binder-disintegrant, compactibility, psyllium husk, Heckel equation.

INTRODUCTION

An excipient is the component other than active ingredient; added to the formulation to perform an intended function. Investigation of the functionality of an excipient is a challenging task. Functionality of any excipient depends on many attributes such as physical form and properties of excipient, the processing method adopted and interaction of excipient with other components of the formulation. Therefore the specifications for an excipient to be used in the particular formulations has to be established during the formulation development work. As per the proceedings of the international symposium (IPEC-2002), functionality testing of an excipient means direct testing of the concerned function in a particular formulation.[1,2]

Compressibility as well as compactibility are the required properties of the powder / granular blend to be compressed into tablet. Binder confers compactibiliy to the powder bulk and is either dissolved/dispersed in the granulation liquid (granulation binder) or blended in the dry state with other components (dry binder). For poorly compressible material adoption of wet granulation technique to prepare its tablet is essential. After evaporating the granulation fluid, added binders produce dry granules having desired properties like free flow, compressibility and more particularly compactibility.[3] Disintegrant is an agent added in the tablet formulation; that bursts/disintegrants the tablet when kept in dissolution medium. Established disintegrants/ superdisintegrants possess only disintegrating ability and they rarely assists in compactibility of powder blend except starch.[4-6] Starch is used as binder and /or disintegrant in tablet formulations but has to be added in high proportion to get its duel functionality.[3]

Amoxicillin trihydrate has poor compressibility index. Thus incorporation of granulation binder in its tablet formulation to improve its compactibility was enviable. In the present work blend of HPMC K100LV and gel obtained by soaking of psyllium husk was investigated as a 'granulation binder-disintegrant'(novel blend) to design and develop dispersible tablets of amoxicillin trihydrate. Granulation-binder is added in the formulation when wet granulation technique is adopted. This technique imparts compactibility to the powder bulk. The 'novel

granulation binder-disintegrant' was investigated for its functionality in formulation development of dispersible tablets of amoxicillin.

MATERIALS AND METHODS

Materials

Amoxicillin trihydrate and Hydroxypropyl methyl cellulose K100LV were received as gift samples from Ranbaxy Laboratories Limited, Himachal Pradesh. Psyllium husk was authenticated by Agharkar Research Institute, Pune and gel was prepared in the laboratory. Aspartame was obtained as a gift sample from VerGo Goa. Magnesium stearate was procured from Research Lab, Mumbai.

Method of preparation of blend of HPMC K1OO LV and gel of Psyllium husk as granulation binder-disintegrant

The Psyllium husk powder was soaked in demineralised water for 1 hr and added to it HPMC K1OO LV in proportion 1:1 by weight. Both were allowed to hydrate and interact with each other for 12 hrs. After 12 hrs the blend was microwave dried for 5 min at 320 mW to obtain dry powder which was used as 'granulation binder- disintegrant' (novel blend) in further study.

Preparation of granular blend

Granules of amoxicillin trihydrate were prepared by using 10% and 15% novel blend as per composition reported in Table 1. All the ingredients were weighed separately and mixed thoroughly for 10 minutes to ensure uniform mixing in geometrical ratio. The granules were prepared by wet granulation method by using isopropyl alcohol as granulating agent. The granules were evaluated for bulk properties and the results are reported in Table 2.

Table 1: Composition of granular blends.

Ingredients (mg/ tablet)	Batch Code	
	B1	B2
Amoxicillin Trihydrate	125	125
Novel blend	12.5	18.75
Magnesium stearate	1	1
Aspartame	1.5	1.5

Table 2: Results of evaluation of granules.

Code	Bulk density (g/ml)*	Tapped density (g/ml)*	Carr's index (%)*	Hausner Ratio*	Angle of repose (°)*
B1	0.43±0.09	0.50±0.03	14.00±0.18	1.16±0.14	27.74±0.26
B2	0.45±0.07	0.52±0.12	13.46±0.10	1.15±0.19	26.46±0.34

**All values was expressed as Mean ± SD (n=3)*

Investigation of functionality of novel blend as a 'granulation binder'

The 'granulation binder' property of the novel blend was investigated by verifying the Heckel equation (Eq.^{n}1).[7]

$$\ln (1/1\text{-}D) = KP+A \text{ ……. Eq.}^{n}\,1$$

Where, D = Relative density of granules, P = Applied pressure, A = Constant suggested to reflect particle rearrangement and fragmentation, K = Slope of the linear part of the relationship which reflects the deformation of particle during compression.

The granules prepared as per the composition reported in Table 1. The tablets were prepared by applying gradually increasing compression pressures from 1,2,3 and 4 tons. The tablets were evaluated for physicochemical properties and the results are reported in Table 3.This data was used for verification of Heckel equation.

Table 3: Physical properties of the tablets prepared for Heckel treatment.

Code	Compression pressure (tons)	Av. Height (cm) H_1	Av. Weight (gm) W_1	ln (1/1-D)
B1	1	0.311	0.141	3.38
	2	0.308	0.141	3.68
	3	0.306	0.141	3.99
	4	0.304	0.141	4.32
	Highest	H_2= 0.300	W_2= 0.140	
B2	1	0.303	0.147	2.74
	2	0.298	0.147	3.02
	3	0.293	0.147	3.43
	4	0.289	0.147	4.03
	Highest	H_2= 0.286	W_2= 0.148	

Investigation of functionality of novel blend as a 'disintegrant'

The tablet batches (D1 to D6) were prepared as per the composition reported in Table 1 containing 10% granulation binder. The difference in these formulations was based on particle size distribution of the novel blend and compression pressure applied to prepare the tablets as reported in Table 4.[6] Disintegration time and wetting time of tablets of formulations D1 to D6 were measured

in various dissolution media of different pH and the results are reported in Table 5.[8]

Table 4: Details of process and formulation variables to investigate mechanism of disintegration.

Formulation Code	Description of variable	
	Particle size distribution of novel blend (µm)	Compression pressure applied (in tons)
D1	180-150	1
D2	180-150	4
D3	150-125	1
D4	150-125	4
D5	125-106	1
D6	125-106	4

Table 5: Results of evaluation of tablets for disintegration time.

Code	Medium used	Wetting time* (sec)	Disintegration time* (sec)
D1	Distilled water	6±1	10±2
	0.1 N HCl	16±1	19±2
	0.1 N NaOH	18±1	20±2
D2	Distilled water	7±2	10±2
	0.1 N HCl	9±2	14±2
	0.1 N NaOH	14±2	17±2
D3	Distilled water	9±1	14±2
	0.1 N HCl	11±1	16±2
	0.1 N NaOH	14±1	18±2
D4	Distilled water	8±1	12±1
	0.1 N HCl	7±1	12±1
	0.1 N NaOH	6±1	16±1
D5	Distilled water	Instantaneous wetting and dispersion	Instantaneous wetting and dispersion
	0.1 N HCl	Instantaneous wetting and dispersion	Instantaneous wetting and dispersion
	0.1 N NaOH	Instantaneous wetting and dispersion	Instantaneous wetting and dispersion
D6	Distilled water	6±2	28±2
	0.1 N HCl	9±2	26±2
	0.1 N NaOH	17±2	34±3

*All values was expressed as Mean ± SD (n=3)

Preparation and evaluation of dispersible tablets of amoxicillin trihydrate by 2^2factorial design

A 2^2 factorial design was implemented to study the effect of formulation and processing variables on the performance of dispersible tablet formulation of amoxicillin trihydrate. According to the model it contained 2 independent variables at 2 levels, +1,-1 and reported in Table 6 and 7. According to model total four formulations are possible, the composition of different formulation are shown in Table 8. The different independent variables were amount of novel 'granulation binder-disintegrant' (X1) and compression pressure (X2). Dependent factors included disintegration time and hardness of the tablet. Powder blends were prepared of composition reported in Table 8 and assessed for bulk properties. These blends were compressed in to tablets by applying compression pressures 1 and 4 ton. The tablets of factorial batches were evaluated for appearance, weight variation, wetting time, disintegration time and hardness. The results are reported in Table 9.

Table 6: Factorial design for preparation of batches.

Batch code	Variable Level in Coded Form	
	X1	X2
F_1	-1	-1
F_2	-1	+1
F_3	+1	-1
F_4	+1	+1

Table 7: Translation of Coded Value in Actual Unit.

Variable level	Low (-)	High (+)
X1= % of granulation binder- disintegrant	10	15
X2= Compression pressure in tons	1	4

Table 8: Composition of factorial batches.

Ingredients (mg/tablet)	Formulation code			
	F1	F2	F3	F4
Amoxicillin trihydrate	125	125	125	125
Granulation binder-disintegrant (X1)	12.5	12.5	18.75	18.75
Aspartame	1.5	1.5	1.25	1.25
Magnesium stearate	1	1	1	1
Compression Pressure in tons (X2)	**1**	**4**	**1**	**4**

Table 9: Data for responses of factorial formulations.

Formulation code	Response parameter	
	Disintegration time* (Sec)	Hardness* (N)
F1	12±2	30±4.2
F2	12±2	35±3.5
F3	13±2	33±2.4
F4	14±2	34±3.2

*All values was expressed as Mean ± SD (n=3)

RESULTS AND DISCUSSION

Preparation of granular blend

Results reported in Table 2 revealed that the granular blend of composition B1 and B2 possessed good compressibility and flowability as evident by compressibility index between 13.46% to 14% and angle of repose between 26.46% to 27.74%.[9]

Investigation of functionality of novel blend as a 'granulation binder'

Heckel treatment was given to the data generated as reported in Table 3.The linear relationship observed between ln(1/1-D) and applied compression pressure (Figure 1) for B1 and B2 prepared by adding novel blend in proportion 10% and 15% respectively. Thus functionality of novel blend as a granulation binder was confirmed.[10]

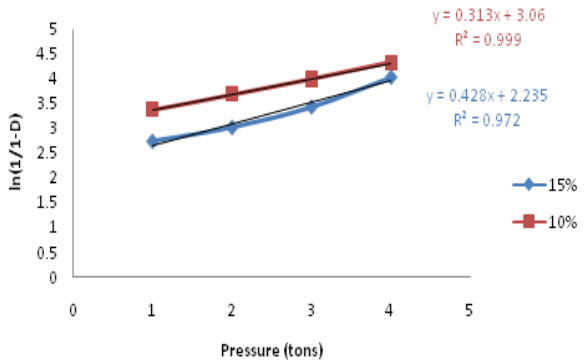

Fig. 1: Heckel plot.

Investigation of functionality of novel blend as a 'disintegrant'

It is reported in the literature that Psyllium husk powder swells on hydration and disintegrats evenly when added as a disintegrant in the tablet formulation .[11]In the present study it is blended with HPMC K100 LV to achieve multi functionality of blend as a granulation binder-disintegrant. To investigate the functionality of novel blend as disintegrant the particle size distribution of novel blend, compression pressure applied to prepare the tablets and the composition of disintegration medium were intentionally varied. Effect of these variables on the disintegration time of the tablets was studied to decide mechanism of disintegration of novel blend. The work was planned and executed as per the procedure reported by Bele and Derle 2012.

The results of experiments (Table 5) indicated that as compression pressure applied during compression of tablet was increased; the disintegration time was decreased except at high compression pressure with least particle size distribution. As the particle size distribution decreased the disintegration time was found to be decreased. Considering both these aspects; it was concluded that the predominant mechanisms for disintegration of novel blend was swelling and deformation. All the disintegrants fundamentally disintegrate by swelling mechanism. The novel blend used in this study exhibited disintegration by deformation along with swelling. The fact that tablets prepared by using novel blend with least particle size distribution and applying high compression pressure (formulation D6) exhibited delayed disintegration may be justified as follows. The dual functionality of the novel blend as 'granulation 'binder-disintegrant'was proposed in this work. It was observed that when the particle size of the novel blend was least; the compression pressure applied to prepare tablets had considerable impact on the mechanism disintegration of the tablets. At lower compression pressure (D5) tablet (which was of same composition as D6) was not hard enough and dispersed immediately. Novel blend with least particle size when used in tablet formulation and prepared by applying high compression pressure (D6); due to its uniform distribution in the tablet imparted more compactibility to the tablet resulting in its delayed disintegration.

Preparation and evaluation of dispersible tablets of amoxicillin trihydrate by 2^2factorial design

The Hausner ratio of granular blend of factorial batches was found to be in the range 1.22 to 1.23 and angle of repose was between 27.74 to 28.48. These results revealed that the compressibility as well as flowability of granular blend was good.[9] The tablets of factorial batches prepared as per the reported procedure and composition were off white colored, round with smooth surface with weight variation within acceptable limits.[8]

Regression analysis

The data obtained after evaluation of factorial batches was analysed by using commercially available software Design Expert version 10. To describe the response surface curvature, the design was evaluated by quadratic model, which bears the form of equation (Eq^n. 2)

$$Y=b_0 + b_1X1 + b_2X2 + b_1\,b_2\,X1X2 + b_1{}^2X1^2 + b_2{}^2X2^2 \ldots\ldots\ldots\ldots Eq^n\ 2$$

Where **Y** is the response variable, $\mathbf{b_0}$ the constant, an arithmetic mean of all responses, $\mathbf{b_1}$, $\mathbf{b_2}$ the regression coefficients, $\mathbf{b_1^2}$, $\mathbf{b_2^2}$ are the regression coefficients show linearity, **X1** and **X2** stand for the main effect, **X1X2** are the interaction terms, show how response changes when two factors are simultaneously changed.

A. Effect of independent variables on Disintegration time

The polynomial equation obtained was-

$$\text{Disintegration Time } (Y_1) = +13.00+0.67X1+0.33X2+0.33X1X2\ldots\ldots\ldots Eq^n\ 3$$

As amount of binder disintegrant increased, disintegration time was increased as indicated by positive coefficient of X1. As the compression pressure increased the disintegration time was increased as indicated by positive coefficient of X2. The interaction between the factor X1 and X2 was observed and both were found to add the effect of each other and was obvious by positive coefficient of X1 X2. The surface response plot is shown in the Figure 2.

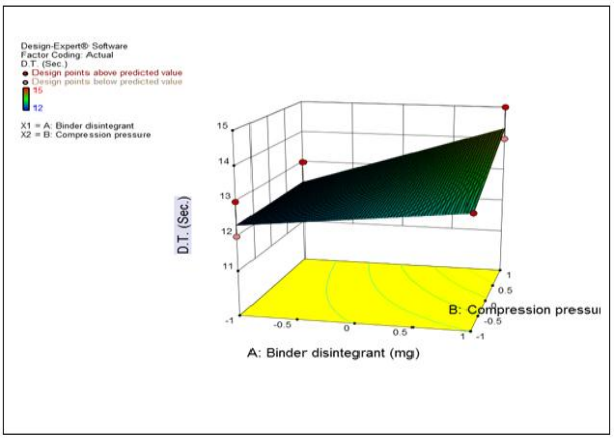

Fig. 2: Response surface plot showing effect of formulation variables on disintegration time.

B) Effect of independent variables on Hardness

The polynomial equation obtained was-

Hardness (Y_2) =

+33.75+0.25X1+ 2.08X2- 1.08X1X2……..Eq^n 4

The hardness of the tablet was increased as the amount of amount of binder disintegrant was increased as indicated by positive coefficient of X1. Also, with increased compression pressure hardness proportionally increased as indicated by positive coefficient of X2. The interaction between the factor X1 and X2 was observed and both were found to negate the effect of each other. It was obvious by negative coefficient of X1 X2. Negative interaction might be due to dual functionality of novel blend as granulation binder and disintegrant. The mechanism of disintegration of this novel bled was found to be swelling and deformation. When the disintegration mechanism of the disintegration is deformation; tablet prepared at high compression pressure disintegrated faster but at the same time hardness increased as novel 'granulation binder-disintegrant' imparted more compactibility. The surface response plot is shown in the Figure 3.

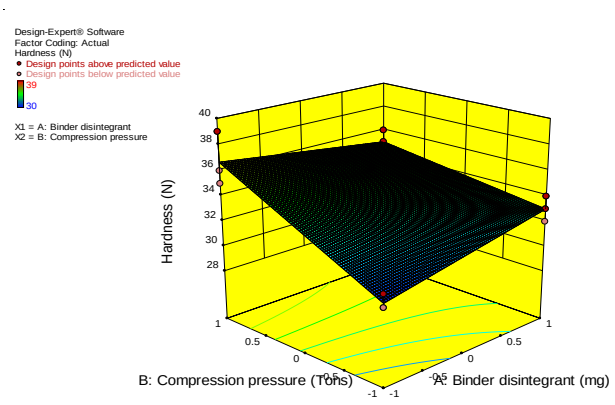

Fig. 3: Response surface plot showing effect of formulation variables on Hardness (Y_2).

CONCLUSION

The novel blend of gel prepared by soaking psyllium husk and HPMC K100LV was investigated for its dual functionality as 'granulation binder-disintegrant'. Granulation binder property of novel blend was confirmed by Heckel treatment and the mechanism of its disintegration was found to be swelling and deformation. This study was planned and executed in accordance with the proceedings of the International symposium held in 2002 at Brussels. The dual functionality was confirmed through the formulation development of dispersible tablets of amoxicillin trihydrate. The formulation of dispersible tablets was optimized by adopting 2^2 factorial design. The regression analysis was used to judge the influence of amount of novel blend added in the formulation and compression pressure applied; on the performance of the formulation. The disintegration time and hardness of factorial batches were measured and the results were analyzed by applying two way 'ANOVA'. The mechanism of disintegration of novel 'granulation binder-disintegrant' was further confirmed during optimization of formulation.

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