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Preparation of Paracetamol Tablets Using PVP-K30 and K90 as Binders

Zafar Iqbal Roohullah[1*], Jamshaid Ali Khan[1], S. M. Asim Daud[2] and Bashir Ahmad Obaidullah[3]

[1]Department of Pharmacy, University of Peshawar, Peshawar-25120
[2]Department of Statistics, University of Peshawar, Peshawar-25120
[3]Faculty of Pharmacy, Gomal University, D.I.Khan

Abstract

Paracetamol tablets were prepared by wet granulation method using PVP K30, PVP K90 and mixture of PVP K30 and PVP K90 as binding agents. The effect of binding agents on the physical characteristics i.e. granule size, bulk density and angle of repose of the paracetamol granules were studied. The analysis of active constituents was followed by the study of weight variation, hardness, disintegration time, friability and dissolution test of all tablet formulations. All formulations comply with the weight variation test. Hardness of the tablets was significantly ($p < 0.05$) increased with increasing the concentration of the binders. Tablets prepared using only PVP K30 (2%) failed the friability test. The maximum disintegration time was 135 seconds and all tablets passed the dissolution test. A good correlation between various physical parameters of granules and tablets was observed. The PVP K90 showed better binding properties compared to the PVP K30 or mixture of PVP K90 and PVP K30.

Key words: Polyvinylpolyvidone, Binding agent, Paracetamol, Granules, Tablets.

Introduction

Polyvidone and Polyvinylpolyvidone (PVP) are used as diluent, binder, disintegrating agent and coating material in tableting technology, and suspending or viscosity building agent in liquid formulations [Martindale, 1989]. Granules prepared using PVP were found to be stronger and less friable compared with the methocel, acacia, and methyl cellulose (Cutt *et al.*, 1986, Joneja *et al.*, 1999). In wet granulation process the surface polarity of both powder and polymer binders are important factors in determining the strength of granules. Binders and powder with similar surface polarities produce strong granules and the degree of polymerization increases the strength of granules (Horisawa *et al.*, 1993, Sinchalpanld, 1993).

The aim of this study was to evaluate the various physical characteristics of granules and tablets formulated using PVP K90 and PVP K30 and mixture of both of these binding agent. The paracetamol tablets were used as model drug.

* *Corresponding author* e-mail: zafariqbal_735@yahoo.com.

Materials and methods

Paracetamol (Army Welfare Pharmaceutical, Lahore)., Lactose (Lactose. Co, Ltd., NewZeeland), Pregelatinized Maize starch,. Dextrose (Rafhan Maize Products Co. Ltd., Faisalabad), CMC-Na (Goto Kuyu Kuhin Ltd., Japan), Avicel (FMC Corp. Philadelphila, USA), Methocel (Dow Chemical Co. Ltd., UK), PVP-K90 and PVP-K30 (BASF Ltd. UK), Talc, Magnesium stearate (Xangping Chemical Works, China).

Instrumentation: Oscillating granulator (F.D & C Karachi, Pakistan), Z.P 19 Rotary Tablet Press (STC, Shanghai, China), Hardness Tester (model TBH 28, Erweka, Germany), Disintegration Test Apparatus (model ZT 3 Erweka, Germany), Dissolution Test Apparatus (VEEGO AD-6D, USA), Friabilator (Erweka, Germany).

Preparation of tablets The batch of 2 kg (paracetamol) was prepared for each formulation in triplicate with varying amount and combination of binders as shown in Table 1.

Table 1. Composition (mg/tablet) of paracetamol formulations.

Ingredient	**Formulation**								
	K1	K2	K3	K4	K5	K6	K7	K8	K9
Paracetamol	500	500	500	500	500	500	500	500	500
PVP K30	-	-	-	10	20	25	10	10	5
PVP K 90	5	7.5	10	-	-	-	5	10	10
Starch *	35	35	35	35	35	35	35	35	35
Mg.Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

*starch powder used as disintegrant

Preparation of granules: Paracetamol and starch were passed through the sieve No. 16 and mixed for 20 minutes using laboratory scale twin cone mixer. The accurately weighed quantity of binder was then dispersed in de-ionized water with continuous stirring and heated until a clear solution was obtained. The binder was then slowly incorporated by spreading all over the powder and kneaded with electric hand blender for 20 min to obtain a damp mass. The damp mass was passed through an oscillating granulator fitted with a # 8 screen and dried in tray dryer at 60°C for 1h. The dried material was then passed through oscillating granulator equipped with a # 12 screen.

Tableting: All the granules were lubricated with talc and magnesium stearate and compressed using ZP 19, rotary press, equipped with 12 mm flat rounded beveled edge punches. The following parameters were studied for granules and compressed tablets.

Angle of repose for the granules : The angle of repose (tan_{α}) was determined by cone angle method (Parrott and Saski 1977) in triplicate. The granules were passed through an 8-mm orifice. The tangent of the repose was determined from the height and radius of the cone ratio.

Bulk density of granules : An accurately weighed sample (M) of granules was carefully added to graduated cylinder through a funnel (Ritala *et al.*, 1987). The initial volume was recorded and then the sample was tapped until no further reduction in volume was observed. The volume at the tightest packing i.e. V_b was used for the calculation of bulk density (ρ_b) according to the formula

$$\rho_b = M/V_b$$

Sieve analysis: The average granule size and its distribution were determined in triplicate by sieving through a set of US standard sieves (334, 701, 883, 1168 and 1397 mm) as described elsewhere (B.P. 1998). The average granule size was presented as geometric mean.

Weight variation and hardness of the tablets: Weight variation of the various formulations of the tablets were determined according to B.P. (B.P. 1998) using a 2842-Sartorius analytical balance with the precision of 0.05 mg and readability of 0.1 mg.

Hardness: The hardness of the tablets was measured for 20 tablets from each batch using Erweka Hardness Tester D-6072 Dreieich, made in Germany), numeric values were noted on scale during breaking in newton.

Disintegration time: The disintegration time of tablets was determined at 37 ± 1°C according to the method described in the British Pharmacopoeia, 1998.

Dissolution of the tablets: The dissolution test of the tablets was performed at 37 ± 1°C according to British Pharmacopoeia, 1998 using Erweka-DT dissolution tester (Made in Germany) equipped with basket assembly. Distilled water (900 ml) was used a medium.

Friability of tablets: The friability of the tablets (n = 10) was determined using friability tester (Erweka-TA; Made in Germany). The friabilator was rotated for 100 revolutions. The friability was expressed as percentage loss due to abrasion or fracture.

Statistical analysis: Statistical analysis was carried out using "Minitab" a statistical package. The significant difference was measured using student-t test (at 95% confidence interval) and one way ANOVA. The average granule size is presented a geometric mean. The correlation between the various parameters was multiple correlation and regression analysis.

Results and Discussion

Paracetamol granule: The size of the granules were increased with increasing the amount of either PVP K90, PVP K30 or their combination. The physical characteristics of the granule are shown in table 2. However, only PVP K90 (2%) produced significantly larger granules compared with the other formulations ($p > 0.05$). Generally, the higher ratio of binders results in the large granule size (Ritala *et al.*, 1987) and these formulations followed the similar pattern. The correlation between the concentration of the PVP K90 and PVP K30 and size of the granule was 0.979 and 0.986, respectively (Table3-4). These results indicates that amount of the PVP K30 and PVP K90 when used as a binder have an prominent impact on the granule size. The regression analysis shows that PVP K90 have more impact on the granule size compared with the PVP K30.

The angle of repose for all formulations was between 20° and 23° that indicate free flowing properties of granules (Rowe, 1989) having mono size, spherical shape with smooth surfaces (Cutt *et al.*, 1986). Angle of repose steadily increased with increasing the concentration of PVP K90 (Table 4) and the high correlation value (0.97) between angle of repose and the amount of binder was observed. The mixed binders showed the similar results (Table 5). The correlation between the different concentrations of PVP K30 and angle of repose, and mixture of the PVP K90 and PVP K30 was weak compared to the PVP K90 (Table 3). The angle of repose for all of the formulation were in the good range to provide free flow properties to the granules during compression that shows that angle of repose is independent of concentration and type of PVP binders.

Bulk density of the granules was significantly increased ($p < 0.05$) with increasing concentrations of the PVP K90 (Table 3) and good correlation was observed between the

concentration of PVP K90 and bulk density (0.961). The correlation between the concentration of the binding agents and the bulk density in formulations containing PVP K30 and mixture of PVP K30 and PVP K90 as binder was poor (Table 5).

Paracetamol tablets: The mass of the tablets of all formulations were in the range of 0.539-0.573 g and were within the limits of BP i.e. ± 5 % (B.P. 1998). The difference between weight of the tablets among various groups was determined using ANOVA test. The mass of the tablets containing PVP K90 (1%) were significantly higher ($p > 0.05$) compared to the other formulations in the same groups. This may be due to the physical characteristics of the granules of the respective batches.

It was found that increasing the concentration binders followed the significant increase in hardness ($p > 0.05$) of the tablets. The correlation between the concentration of binders (both PVP K90 and PVP K30) and hardness of the tablets was positive (Table 3). The formulation containing the mixture of PVP K90 and PVP K30 showed the vague relationship with the hardness of the tablets (Table 3). The regression analysis shows that the concentration of PVP K90 have greater and significant ($p < 0.05$) impact on the hardness of the tablets compared with the PVP K30.

The loss during friability test was less than 1% in all formulations except PVP K 30 (2%) where loss was 1.2 %. The loss during friability was found to be negatively correlated with the concentration of PVP K90 and PVP K30 (Tables 3-4). The friability of the PVP K30 preparations also showed the similar correlation pattern as observed for PVP K90. Howevet, the concentration of the mixed binders gave the positive correlation with friability of the tablets.

Disintegration time of all the formulations were within official limit (B.P. 1998) i.e. less than 15 minutes and data was in good agreement with other studies (Visavarugnroj and Remon 1990) The positive but weak correlation with various parameters studied for granules and tablets was observed for all preparations except the mixed binding agents. Typically good correlation was found between the disintegration time and concentration of PVP K30. Thus, good disintegration time was obtained using PVP as a binder.

Dissolution test was carried out using basket method (B.P. 1998). All the preparations passed the dissolution test. The formulations containing the PVP K90 were negatively correlated to the concentration of the binder (Table 3) while no correlation was observed between the concentration of PVP K30 and dissolution time. The mixed binding agent gave the vague correlation with the dissolution of the tablets.

The present studies shows that PVP K30 and PVP K90 are good binders for the tablets, both binders furnishes the granules and tablets of good physical characteristics. Only those preparations containing the PVP K30 (2%) failed the friability test but it can be controlled either by increasing the concentration of the binder (as observed) or by increasing the hardness of the tablets, if possible. The PVP K90 showed better correlation with granule size, angle of repose and density of the granules and, negative correlation with the friability and dissolution test of the tablets compared to the PVP K30. The use of mixture of PVP K90 and PVP K30 did not furnishes desirable results compared with the use of individual PVP K90 and PVP K30 binders.

Table 2. Physical Characteristics of paracetamol granules and tablets

Formulation	Composition	Particle Size	Angle of Repose	Density	Hardness	Friability	D-Time	Dissol.T (45 min)	Wt. of Tab. (mg)
K1	PVP-K90 (1.0)	692.47	20.55	0.575	65.60	0.98	15	99.2	573
K2	PVP-K90 (1.5)	694.33	21.34	0.577	67.35	0.99	30	98.2	563
K3	PVP-K90 (2.0)	698.26	22.34	0.583	73.41	0.77	90	96.4	563
K4	PVP-K30 (2.0)	693.73	20.02	0.555	61.00	1.20	15	98.4	539
K5	PVP-K30 (4.0)	696.13	22.07	0.553	68.23	0.72	60	97.0	560
K6	PVP-K30 (5.0)	698.33	22.02	0.554	94.77	0.62	75	96.3	555
K7	PVP-K30: K90 (2.0 :1.0)	705.96	19.71	0.553	75.61	0.78	15	95.4	561
K8	PVP-K30: K90 (2.0 :2.0)	697.73	20.18	0.554	88.87	0.55	135	95.0	564
K9	PVP-K30: K90 (2.0 :1.0)	693.21	21.01	0.553	78.10	0.63	85	98.0	563

Table 3. Correlation of various parameters of paracetamol granules and tablets of formulations containing PVP-K90 as a binder.

	Conc.	Granule Size	Angle of Repose	Density	Hardness	Friability	D-Time	Dissolution.
Granule size	0.979							
Angle of Repose	0.970	0.999						
Density	0.961	0.997	0.999					
Hardness	0.955	0.995	0.998	1.00				
Friability	-0.845	-0.963	-0.950	-0.960	0.966			
D-Time	0.866	0.747	0.719	0.693	0.678	0.465		
Dissolution	-0.976	-1.00	-1.00	-0.998	-0.996	0.941	-0.737	
Wt.	-0.866	-0.747	-0.719	-0.693	-0.678	0.465	-1.00	0.737

Table 4. Correlation of various parameters of paracetamol granules and tablets of formulations containing PVP-K30 as a binder

	Conc.	Granule Size	Angle of Repose	Density	Hardness	Friability	D-Time	Dissolution
Granule size	0.986							
Angle of Repose	0.938	0.868						
Density	0.756	0.853	0.481					
Hardness	0.873	0.941	0.649	0.979				
Friability	-0.985	-0.944	-0.983	-0.633	-0.777			
D-Time	0.996	0.967	0.965	0.693	0.825	-0.997		
Dissolution	-0.099	0.066	-0.439	0.577	0.399	0.267	-0.189	
Wt.	0.845	0.746	0.978	0.289	0.477	-0.924	0.890	-0.615

Table 5. Correlation of various parameters of paracetamol granules and tablets of formulations containing mixed binders (PVP-K90 and PVP-K30).

	Granule Size	Angle of Repose	Density	Hardness	Friability	D-Time	Dissolution
Angle of Repose	-0.948						
Density	-0.166	-0.158					
Hardness	-0.337	0.019	0.984				
Friability	0.760	-0.513	-0.766	-0.868			
D-Time	-0.637	0.357	0.866	0.941	-0.985		
Dissolution	-0.687	0.863	0.603	-0.452	-0.051	0.123	
Wt.	-0.936	0.775	0.501	0.647	-0.940	0.867	0.386

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