EFFECT OF STARCH 1500 AS A BINDER AND DISINTEGRANT IN LAMIVUDINE TABLETS PREPARED BY HIGH SHEAR WET GRANULATION

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ABSTRACT

High shear wet granulation is a preferred manufacturing method of tablets. It allowed for rapid production of compressible granulations. The resultant granulation characteristics depend on a combination of formulation properties and processing parameters. Fully pregelatinized starches are currently being used as binders in wet granulated formulations. But due to the gelatinization, much of the disintegration properties are lost. Partially pregelatinized starches (Starch 1500) have a mixture of properties of both native and fully gelatinized starches; made them useful as both a binder and a disintegrant in wet granulated formulations. Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced Lamivudine tablets of improved hardness and friability compared with those prepared with povidone. The formulation of Lamivudine tablets with Starch 1500 exceeded the disintegration and dissolution performance of the povidone formulation that utilized a super disintegrant. High shear wet granulation is also well suited for the use of partially pregelatinized starches.

Keywords: Starch 1500, binder, disintegrant, lamivudine tablets, wet granulation.

INTRODUCTION

The majority of formulations in the development of new drug products contained maize starch that was used as a both binder and disintegrant (Herbert *et al.,* 1989). But now present days, its use was limited because the starch lost much of its disintegration properties when it gelatinized in the preparation of the starch paste (Colorcon, 2005). As a dry addition to the granulation, the maize starch did not flow well and was not very compressible.

Today, polymers such as povidone are preferred as binders for wet granulated products. When hydrated these binders produce viscous, tacky solutions. The tackiness holds the individual granules together. Added dry to a granulation polymers aid in the agglomeration of fine powders upon addition of an appropriate solvent to the granulator. However, polymer binders can also lead to processing difficulties such as rapid over granulation. Over time they occasionally lead to tablet hardening and a decrease in dissolution performance (Colorcon, 2005; Moore and Flanner, 1996).

A balance must be maintained between the binding and the disintegration properties of a formulation. When polymer binders are chosen, the addition of strong disintegtants such as super disintegrants is typically required but these are considerably expensive and have a negative effect on product stability as well as film coating appearance of the finished products (Levina and Cunningham, 2005). An alternative to maize starch and polymers for wet granulations is pregelatinized starch that is a starch that has been previously gelatinized and dried to powder form (Cunningham *et al.,* 1999; Anastasiades *et al.,* 2002).

Lamivudine (2',3'-dideoxy-3'-thiacytidine, commonly called 3TC) is a potent oral nucleoside analog reverse transcriptase inhibitor (nRTI) has demonstrated efficacy against the hepatitis B virus (HBV) in both HBeAg-positive and HBeAg-negative patients with chronic hepatitis B. Treatment with lamivudine is safe and well tolerated and induces a virological and biochemical response in most patients within a short time. In 1998, lamivudine became the first commercially available oral agent for the treatment of chronic hepatitis B. Lamivudine is a synthetic nucleoside analogue that undergoes intracellular phosphorylation to its active metabolite, lamivudine triphosphate. Unlike interferon, lamivudine has direct antiviral activity and is a powerful inhibitor of HBV reverse transcriptase (Doong *et al.,* 1991). Lamivudine has been used for treatment of chronic hepatitis B at a lower dose than for treatment of HIV. Long term use of lamivudine unfortunately leads to emergence of a resistant hepatitis B virus (YMDD) mutant. Despite this, lamivudine is still used widely as it is well tolerated.

Wet granulation is a commonly used method used in the manufacture of tablets, which improves the tabletting process via the production of a product (granulate) that has

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improved flowability, uniformity and compressibility when compared to original drug containing powder blend. There are many methods used in the pharmaceutical industry to produce granules however the most common is high shear. As with most pharmaceutical processes wet granulation is a complex one, in which many factors such as binder used and processing conditions will influence the physical properties of the resultant granule. The object of this exercise is to develop an optimum granule in terms of compression properties and flowability in the short time available without considering the numerous variables in great detail. The approach is to screen a number of disintegrants and binders on the small scale and assess the product for physical and chemical characteristics.

This study compared the high shear wet granulation and tablet properties of two formulations of Lamivudine. One is based on a polymer, povidone in combination with a super disintegrant, sodium starch glycolate. Another formulation utilized partially pregelatinized maize starch as both the binder and the disintegrant.

MATERIALS AND METHODS

Materials

Table 1 listed the formulations evaluated for this study. Lamivudine USP (Hetero Drugs Ltd. India) was kind gift from Square Pharmaceuticals Ltd. Bangladesh. The excipients were present in the tablets: microcrystalline cellulose or Avicel pH 102 (Angel Associate, Taiwan), povidone BP (Kollidon 30; BASF), pregelatinized starch (Starch 1500; Colorcon), sodium starch glycolate (Yung Zip Chemical Ltd. Taiwan) and magnesium stearate (Peter Greven, c.v. Netherlands).

Methods

The granulation process was carried out in TK Fielder PMAT-10 (Niro Inc). The batch size was 2.5 kg for each trial. Materials were preblended for 5 minutes prior to granulating with an impeller of 250 rpm and chopper speed setting of II. Drying was done using fluid bed drier with an inlet of 60^{o}C. Each batch was dried to moisture content about 2% w/w which was close to the preblend LOD measured earlier.

Final sizing of the granulations was performed by hand, using a 20-mesh screen. Granules were manufactured and physically characterized by measuring, particle size distribution, angle of repose (Banker and Anderson, 1986), and bulk and tapped density (Phadke and Anderson, 1990). Hausner factor, the ratio of tapped density to poured density, was also studied and calculated for the tested granules as evaluation parameters for compressibility. Particle size distribution of the granules was determined by sieve analysis using 30 g of the granules. Series of US standard sieves ranging in screen opening from 315 to 800 µm were used. The granules were placed on the top sieve and were mechanically shaken for 10 minutes on a shaker (Rota C30, Germany). The fraction retained on the sieve weighted and average particle size was calculated (Railkar and Schwartz, 2001).

Lubricants were passed through a 60-mesh screen prior to blending. Blending was performed with a tumbling mixer (Patterson-kelly Twin shell blender. Model LB 331). All ingredients except lubricant were blended for 10 minutes. The efficiency of mixing was verified by determination of drug content. The lubricant was added and blended for an additional 5 minutes.

The produced mixture was compressed into tablets using an instrumented 35-station BB4 tablet compression machine (Manesty, England), fitted with 8mm deep concave tooling; at 23 rpm. The machine was adjusted to produce tablets of 200 mg in weight and each contains 150 mg of Lamivudine. For each formulation a compression profile was generated covering 4 to 20 kN. The tablet properties were evaluated after compression with an Erweka Multicheck using a sample size of 10 tablets. Tablet thickness was done according to USP 30. The experiments were done 6 times and the mean value and standard deviation were calculated. Friability was evaluated at 100 drops using an Erweka Friabulator. Disintegration times were measured according to USP 30 with an Erweka DT bath using deionized water.

Dissolution testing was performed in a USP compliant dissolution bath using apparatus 2 (paddle method) at 50rpm. The apparatus (Erweka) was assembled and one tablet containing 150 mg of Lamivudine was placed in 900 ml of purified water which was warmed to 37 ± 0.5°C previously. After 15 minutes, 10 ml of sample was withdrawn from dissolution medium using glass pipette and filtered with filter paper and replaced immediately with same volume of fresh medium maintained at the same temperature. The withdrawn solution was diluted suitably to achieve the drug concentration 1.66mg/100ml and the amounts of Lamivudine released were determined spectrophotometrically at 272 nm using dissolution medium as a blank. All assays were done in triplicates and the mean values were calculated. This testing was repeated on 30 and 45 minutes.

RESULTS AND DISCUSSION

The prepared granules, using wet granulation method, were evaluated prior to compression into tablets (table 2). The granules with (Formula 2) and without (Formula 1) Starch 1500 showed similar values of for the angle of repose which indicate good flowability. This is also supported by the data of Hausner factor which indicate good flowability for the granules.

Table 1: Composition of the prepared Lamivudine USP 150 mg tablet formulations.

Ingredients	Amount of ingredients used in each tablet formula			
	F (1)		F (2)	
	Percent	Mg/tablet	Percent	Mg/tablet
Wet Granulation				
Lamivudine USP	75%	150.00	75%	150.00
Microcrystalline Cellulose BP (Avicel pH 102)	10%	20.00	-	-
Povidone BP	5%	10.00	-	-
Sodium Starch Glycolate BP (Primojel)	2.5%	5.00	-	-
Starch 1500 (Pregelatinized Starch) NF	-	-	14%	28.00
Dry additions				
Microcrystalline Cellulose BP (Avicel pH 102)	4%	8.00	4%	8.00
Sodium Starch Glycolate BP (Primojel)	2.5%	5.00	-	-
Starch 1500 (Pregelatinized Starch) NF	-	-	6%	12.00
Magnesium Stearate BP	1%	2.00	1%	2.00
Total	100%	200	100%	200

Table 2: Properties of the prepared granules and Lamivudine USP tablets.

Formula No.	Properties of granules				Properties of the tablets		
	Particle size (µm)	Angle of repose	Hausner factor	Moisture content (%)	Mean wt. (mg)	Actual drug content (%)	Mean thickness (mm)
1	517.45	32.15± 0.21	1.15± 0.02	1.98 ± 0.01	202.2 ± 0.22	100.56 ± 0.52	4.21 ± 0.21
2	503.10	33.95± 0.28	1.19± 0.01	1.83 ± 0.02	201.4 ± 0.43	99.56 ± 0.42	4.11 ± 0.33

Formula 1 was listed in table 1 and utilized common granulation excipients. The quantity of each ingredient was chosen to be within the recommended use levels. The granulation contains microcrystalline cellulose (MCC) at approximately 10% internally and 4% externally to the granulation. MCC lost some compactability when used in wet granulations; therefore, it was desirable to incorporate a portion of it externally to ensure good tablet hardness. The dissolution performance of the granulated formulation was improved using super disintegrant both internally and externally to the granulation. Sodium starch glycolate was used at 5% of the formulation and was split equally between the phases.

Formula 2 was listed in table 1 which was developed using Starch 1500 as binder and disintegrant. All povidone, sodium starch glycolate and internal MCC were replaced with Starch 1500. It was an effective disintegrant but not super disintegrant and typically needs to be used at higher levels to gain similar disintegration performance. The level in the external phase was 6%.

Fig. 1 displayed the tablet hardness of the two formulations. Both produced tablets have comparatively acceptable hardness in the compression force 6 kN but Formula 2 produced tablets performed higher hardness than Formula 1 in the upper compression range.

Fig. 2 showed the friability profiles of the produced products. Both formulations produced low friability. Generally the values of the friability were an acceptable value according to the USP 30. For nearly every point, Formula 2 produced lower friability than Formula 1.

Fig. 3 showed the disintegration performance of the two formulations. The values of the disintegration time of the prepared tablets were within the allowable range of the USP 30 for uncoated tablets. But Formula 2 produced disintegration times that were lower than those for Formula 1 containing super disintegrant.

Fig. 4 represented the dissolution profile for both formulations. Although both formulations met the specifications (>70% after 45 minutes) but Formula 2 performed a more rapid release of the drug than Formula 1. This was due to the inclusion of Starch 1500 in the developed formulation. In contrast to Formula 1, Starch 1500 performed not only as a binder but also was an effective disintegrant allowed the tablet to break down at a faster rate. Tablets used to produce dissolution data

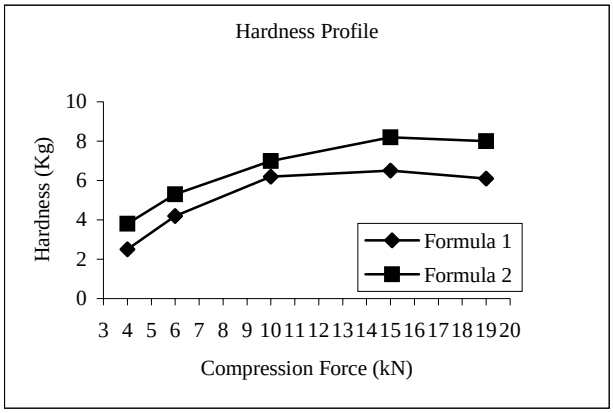

Fig. 1: Hardness profile of prepared Lamivudine tablets.

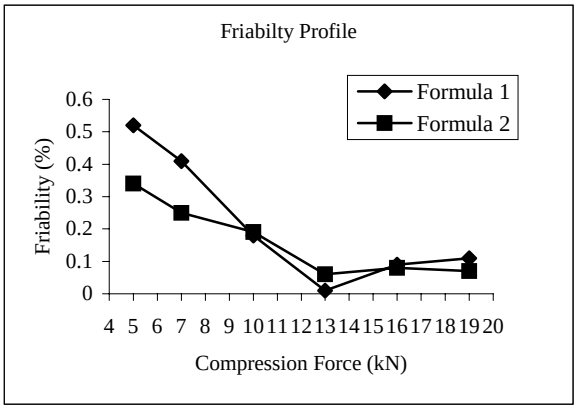

Fig. 2: Friability profile of prepared Lamivudine tablets

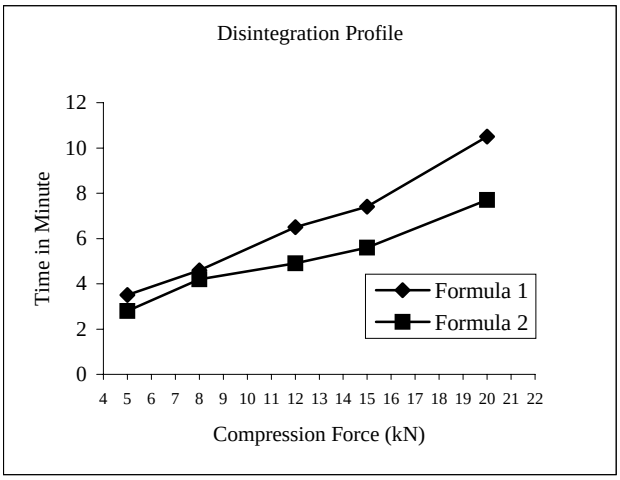

Fig. 3: Disintegration profile of prepared Lamivudine tablets

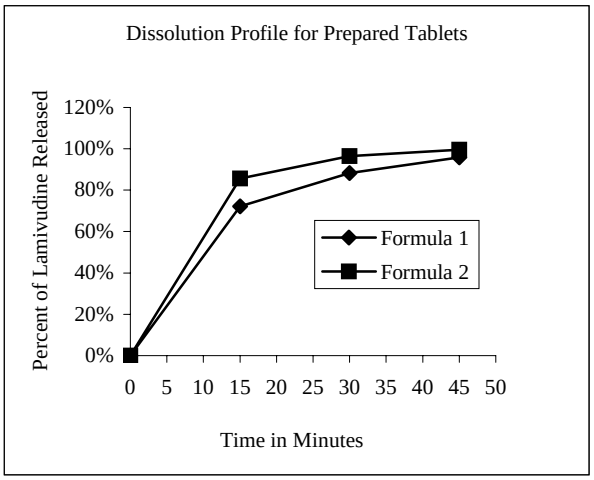

Fig. 4: Dissolution profile of prepared Lamivudine tablets

were compressed at the same force, 10 kN, and produced similar hardness.

The few properties of the finished products are shown in table 2. The following parameters; weight uniformity, drug content and thickness were calculated. Produced tablets were uniformity in weight and thickness; complied the USP 30 requirements. From the obtained data in table 2 in percent of drug contents in prepared tablets were found to be within the range of 99.56 to 100.56% that were within the acceptable limit.

CONCLUSIONS

This study showed the multifunctional properties of partially pregelatinized starch (Starch 1500) in a wet granulation application. Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced tablets of improved hardness and friability compared with those prepared with povidone. Beside these, it has an excellent effect on the disintegration and dissolution performance. This study has shown that Starch 1500 could produce beneficial results while reducing the complexicity of a formulation.

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REFERENCES

Anastasiades A, Thanou S, Loulis D, Stapatoris A and Karapantsios TD (2002). Rheological and physical characterization of pregelatinized maize starches. *Journal of Food Engineering*, **52**(1): 57-66.

Banker GS and Anderson NR (1986). Tablets. In: Lachman L, Lieberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy, Philadelphia, USA: Lea and Febiger Publisher, 293-345.

Colorcon Technical Literature (2005).

Cunningham CR, Kinsey BR and Scattergood LK (1999). Evaluation of a partially pregelatinized starch in comparison with superdisintegrants in a direct-compression hydrochlorothiazide formulation. Poster

presented at the American Association of Pharmaceutical Scientists Annual.

Cunningham CR, Kinsey BR and Scattergood LK (2001). The effect of STARCH 1500 on the stability of aspirin tablets stored under accelerated conditions. Poster presented at the American Association of Pharmaceutical Scientists Annual Meeting in Denver, CO.

Doong SL, Tsai CH and Schinazi RF, Liotta DC and Cheng YC (1991). Inhibition of the replication of hepatitis B virus in vitro by 29,39-dideoxy-39-thiacytidine and related analogues. *Proc. Natl. Acad. Sci.*, **88**(19): 8495-8499.

Herbert AL, Lean L and Josoph BS (1989). Pharmaceutical dosage forms, tablets, 2nd edition, Marcel Decker, New York, pp.209-210.

Krishna SM, Avinash MC, Hyo YK and Ralph FS (1969). Tableting Properties of a Directly Compressible Starch. *J. Phar. Sci.*, **58**: 616-620.

Levina M, Taylor J and Rajabi-Siahboomi AR (2001). The influence of Starch 1500 on drug release from HPMC matrices. AAPS National Meeting.

Levina M and Cunningham CR (2005). The effect of core design and formulation on the quality of film coated tablets. *Pharmaceutical Technology Europe*, **17**(4): 29-37.

Moore JW and Flanner HH (1996). Mathematical Comparison of Dissolution Profile. *Pharm. Tech*., **20**(6): 64-74.

Phadke DS and Anderson NR (1990). Effect of crosspovidone on the wet granulation aspects of acetaminophen. *Drug Dev. Ind. Pharm.*, **16**: 983-994.

Railker AM and Schwartz JB (2001). The effects of formulation factors on the moist granulation technique for controlled release tablets. *Drug Dev. Ind. Pharm.*, **27**: 893-898.

Wanczinski BJ, Felipe DF, Cardoso ML and Cavalcanti OA (2002). Development of AAS 500 mg tablets: Effect of Starch 1500 on direct compression. *Acta Scientiarum*, **3**: 649-655.