Polyvinyl Alcohol Grafted Polyethylene Glycol Copolymer for Application in Floating Drug Delivery Systems

Shaukat Ali, Carlos Santos, and Anisul Quadir

BASF Corporation, Pharma Solutions, 1705 US HWY 46 W, Ledgewood, NJ 07852

Dietary Supplements
- Carotenoids
- Vitamins
- Health Ingredients
- Innovative Applications

BASF
The Chemical Company

Abstract

Grafted polyvinyl alcohol copolymers have been investigated for use in a wide range of pharmaceutical applications. This work was aimed at identifying attributes of the copolymer of polyvinyl alcohol grafted with polyethylene glycol and its combination with 40% polyvinyl alcohol leading to higher performance as binders and matrices for the development of floating drug delivery systems.

Keywords: excipient, floating dosages, drug delivery, polyvinyl alcohol, polyethylene glycol-polyvinyl alcohol, graft copolymer, Kollicoat® IR and Kollicoat® Protect.

Introduction

Floating drug delivery systems (FDDS) have been the subject of continued interest in drug delivery.[1] The excipients used in such matrices included ethylcellulose, hydroxymethyl-cellulose, xanthan gum, chitosan, polyethylene oxide, and wax.[2]

FDDS have been categorized to effervescent and non-effervescent systems. The effervescent systems consist of swellable matrices such as hydroxypropyl methylcellulose, ethyl cellulose, chitosan, and Eudragit 100, and effervescent components are sodium carbonate or bicarbonate and citric acid, ascorbic acid, or tartaric acid.[3] These matrices are designed to entrap liberated carbon dioxide in gellified hydrocolloid so that the dosage can float in gastric fluid. The non-effervescent matrices, on the other hand, possess a gelling characteristic with appreciable micro-porosity and air reservoirs which on exposure to gastric fluid yield buoyancy for the floating dosages. Thus, identifying excipients with the appropriate characteristics required to meet floating and stability challenges in design of pharmaceutical dosages is further warranted.

Polyvinyl alcohol (PVA) has been used in pharmaceutical dosages, but its grafted copolymers are relatively unknown in the pharmaceutical dosages.[4] For instance, PVA grafted copolymers of polylactide-co-glycolides and polyacrylic acid, have been developed, however, their application have been limited to non-pharmaceutical applications. In one study, PVA has been used as hydrogel in drug delivery as an emulsifier,[5] but its role in sustained and/or gastroretentive dosage has yet to be investigated.

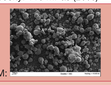
Polyvinyl alcohol (PVA) grafted polyethylene glycol (PEG) copolymer and its combination with PVA (60:40), however, have been studied extensively in film formation for instant release and moisture barrier coatings.[6] Kollicoat® IR, which is a Poly (vinyl alcohol co-ethylene glycol), forms flexible films without requiring plasticizers due, in part, to 25% of PEG in the PVA-PEG copolymer. A recent study suggests that Kollicoat® IR can also be used as a binder in wet granulation.[7].

The present work is aimed at evaluating the copolymer of PVA and PEG (Kollicoat® IR) and its 40% PVA combination (Kollicoat® Protect), as dry binders and as matrices for FDDS in sustained release or extended release dosages.

Experimental Methods

Kollicoat® IR and Kollicoat® Protect were obtained from BASF (Florham Park, NJ). For the excipients used as dry binders, the tablets were prepared by weighing the appropriate amount and direct compression. Unless indicated otherwise, for wet granulations, the granulating agents were sprayed, blended with the appropriate amount and the granules air dried at room temperature over 24 hrs, sieved through USS 20 mesh, and compressed into tablets. The floating characteristics and lag time (t_{lag}), required for the tablet to float, were evaluated. The tablets were compressed on a Carver Press, and the hardness of the tablets was measured on a tablet hardness tester (Key International, Inc., Englishtown, NJ).

Chemistry of Kollicoat® IR and Kollicoat® Protect

Kollicoat® IR	Kollicoat® Protect
	
Structure:	Structure:
Composition: Grafted Copolymer	Composition: Kollicoat® IR 60%
Polyvinyl alcohol 75%	Polyvinyl alcohol 40% (free)
Polyethylene glycol 25%	Silicon dioxide 0.3%
Physical state: Spray dried, white powder	Physical state: Spray dried, white powder
Bulk density: 0.3-0.45 g/ml	Bulk density: 0.22 g/ml
Mean Particle size: 120 microns	Mean Particle size: 125 microns
Mol. Weight: Approx. 45,000	Mol. Weight Approx. 45,000 (Kollicoat® IR) Approx. 35,000 (PVA)
Solubility: Highly soluble in aqueous solutions	Solubility: Highly soluble in aqueous solutions
Viscosity: 115 mPas (20%)	Viscosity: 110 mPas (20%)
SEM: 	SEM: 

Kollicoat® is a registered trademark of BASF AG.

Applications of Koliocoat® IR and Kollicoat® Protect

A: Kollicoat® IR as Instant Release Coating Grafted Copolymer

Figure 1 shows the dissolution of Kollicoat® IR films and compares with HPMC grades Type 3 and Type 6 at pH 1.2 and pH 6.8. The Kollicoat® IR films were soluble at either pH and their solubilities were not affected by changes in pH. Similarly, the HPMC films were soluble at either pH but the dissolution times were 3-4 fold higher than Kollicoat® IR films under identical conditions.

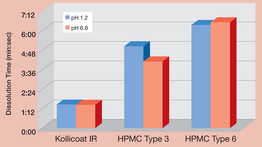


Figure 1: Dissolution of Kollicoat® IR, HPMC (Type 3 and Type 6) films

B. Kollicoat® Protect as a Moisture Barrier

Figure 2 shows moisture protection of Kollicoat® Protect and compares with competitor product and Kollicoat® IR White. The data suggest that Kollicoat® Protect protects against the hydrolysis of acetyl salicylic acid to salicylic acid more effectively than other coatings. This effective moisture protection in the coating as compared to competitor product or others is due, in part, to the 40% free polyvinyl alcohol which prevents permeation of moisture through the films.

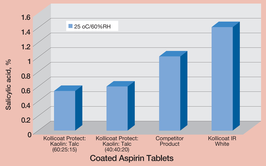


Figure 2: Moisture Protection of Kollicoat® Protect, Competitor product and Kollicoat® IR White

C. Kollicoat® IR and Kollicoat® Protect in Gastroretentive (GR) Dosages

Kollicoat® IR and Kollicoat® Protect, in spite of their instant release and moisture barrier coating applications, have also been examined for their potential use as binders and as matrices for the development of gastroretentive dosages or floating drug delivery systems. Very low levels of peroxide in these excipients also provide an advantage for use as binders.

Results

Kolliocoat® IR and Kolliocoat® Protect as Binders

Previous investigation from our laboratory has shown that, like Kollidon® 30, Kollicoat® IR acts as a good binder in wet granulation, but its performance as a dry binder remains to be further evaluated. Thus, we investigated the binding properties of Kollicoat® IR and of Kollicoat® Protect by direct compression and in wet granulation. The flat faced tablets were evaluated for their hardness, floating characteristics, and lag times.

Figure 3A shows the results from direct compression (DC). The compression data suggests that the hardness of Kollicoat® IR tablets was low (*ca*. 3-4 kP) and essentially unchanged as the compression force increased to 22 kN. In contrast, the hardness of Kollicoat® Protect tablets continuously increased with increasing compression force. At the highest compression force of 22 kN, the hardness of Kollicoat® Protect was about 6 fold higher than that of Kollicoat® IR. Such a phenomenal increase in the hardness of the tablets was evidently due, in part, to significantly large amounts (ca. 40%) of free polyvinyl alcohol in Kollicoat® Protect.

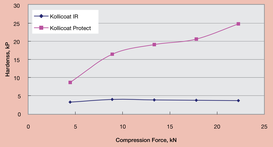


Figure 3A: Effects of comparison force on hardness of dry binders

Figure 3B shows the effect of compression force on the hardness of Kollicoat® IR and Kollicoat® Protect tablets. The compression data demonstrates that the wet granulation was far less effective in Kollicoat® IR than that of Kollicoat® Protect at all compression forces. For instance, the hardness of the Kollicoat® IR remained approx. 5 kP at all compression force, whereas, the hardness of Kollicoat® Protect increased as the compression force was increased to > 18 kN, suggesting that Kollicoat® Protect can act as an excellent binder for DC.

Table I shows the effect of granulation on hardness of Kollicoat® IR and Kollicoat® Protect tablets at different compression forces. The data suggests that wet granulation of Kollicoat® Protect increased the hardness of the tablets nearly 4 times as compared to Kollicoat® IR at all compression forces examined. Although Kollicoat® IR had lower hardness, it showed a relatively higher increase (40-68%) than Kollicoat® Protect at each compression force. Kollicoat® Protect showed a more profound difference at lower compression force (<14 kN) than at higher compression force (>14 kN). For instance, the hardness increased about 119% at 5 kP in Kollicoat® Protect as compared to 59% in Kollicoat® IR.

Table I: Effect of Compression force on hardness of Kollicoat® IR and Kollicoat® Protect granules

Compression Force	Kollicoat® IR, wet granulation (water)		Kollicoat® Protect, wet granulation	
(kN)	Hardness (kP)	Change (%)	Hardness (kP)	Change (%)
5	5.1	59	18.9	119
9	5.5	40	21.0	28
14	6.4	68	22.1	16
18	6.0	61	23.8	15
23	5.5	52	22.7	-9.0

Assessment of Floating Characteristics

Tablets (400 mg each), were assessed for their floating characteristics in water and at pH 1.2 and 7.2. Figure 4 illustrates the lag times in water of the DC tablets of Kollicoat® IR and Kollicoat® Protect. These tablets floated, but some required longer time than others depending on compression force, hardness and matrix composition. For instance, Kollicoat® IR tablets did not show any lag time (t_{lag} = 0) and floated immediately, whereas, Kollicoat® Protect tablets exhibited longer t_{lag} depending upon compression force and hardness. Evidently, the higher compression force increased the hardness, and the t_{lag}. Thus, the Kollicoat® Protect tablets prepared with compression force < 13 kN, showed the t_{lag} < 60 Sec (<1 min), whereas, those prepared with higher compression force >18 kN, significantly increased the t_{lag} > 180 sec (> 3 min) under similar conditions.

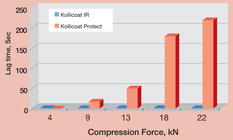


Figure 4: Comparison of lag times of Kollicoat® IR and Kollicoat® Protect

Interestingly, Kollicoat® IR tablets floated immediately (t_{lag} = 0 min), continued floating, and subsequently dissolved within 3-4 hours. Kollicoat® Protect tablets, on the other hand, showed a t_{lag} of 4 min at higher compression force, continued to float over 24 hours, and subsequently dissolved. This marked difference between the two matrices in floating characteristics is attributed due to the low bulk density, micro-porosity and swelling characteristics of PVA in Kollicoat® Protect.

Effects of Granulation on Floating Lag Times

Since Kollicoat® Protect outperformed Kollicoat® IR, further investigations requiring granulations, hardness and lag times were carried out with Kollicoat® Protect. The data (Fig. 5A) show that increasing the amount of Kollicoat® SR 30D to 5% and 10% resulted in a significant increase in t_{lag} at all compression forces. Increasing the t_{lag} likely retarded the floatation by likely increasing swelling and adhesiveness of PVA polymer. The data also shows that increasing the amount of Kollicoat® SR 30D to 10% in the granules did not increase the hardness with increasing compression force.

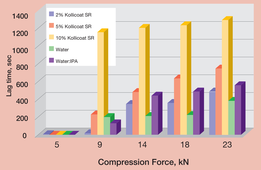


Figure 5A: Effects of granulation on lag time of Kollicoat® IR and Kollicoat® Protect tablets in water

Those tablets evaluated in water as shown in Fig. 5A for their t_{lag} were also evaluated at pH 1.2., as shown in Fig. 5B. The data shows that although the hardness of Kollicoat® Protect tablets remained > 19 kP, the t_{lag} was reduced significantly (3-fold) at pH 1.2 presumably due to less adhesiveness or stickiness of polyvinyl alcohol polymer at lower pH

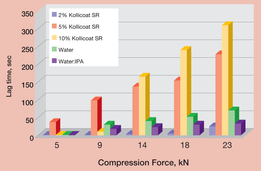


Figure 5B: Effects of granulation on tlag of Kollicoat® Protect tablets at pH 1.2

Figure 5C shows the lag times of the tablets at pH 7.2. The data suggests that Kollicoat® Protect granules showed a short t_{lag} (< 1 min) at all compression force as compared to those obtained at pH 1.2 or water. This difference might be attributed to less adhesiveness/ swelling characteristics of PVA in Kollicoat® Protect.

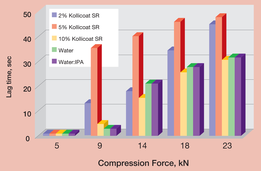


Figure 5C: Effects of granulation on lag time of Kollicoat® Protect tablets at pH 7.2

Discussion

FDDS utilizing non-effervescent excipients such as polyacrylate, polycarbonate, and polystyrene and swellable cellulose based hydrocolloids, polysaccharides have been studied in design and development of gastroretentive dosages. Further endeavor in identifying the excipients less prone to moisture susceptibility and enabling prolonged stability and shelf life of gastroretentive dosages remains a significant challenge. The present study describes the use of PVA based matrices as alternate non-effervescent excipients in the design and development of FDDS.

Polyvinyl alcohol grafted polyethylene glycol copolymer (e.g. Kollicoat® IR) and its combination with 40% PVA (e.g. Kollicoat® Protect) in addition to their instant release and moisture barrier profiles, have been investigated as matrices for direct compressions and wet granulation. Furthermore, because of unique characteristics of possessing low peroxides, appreciable porosities and low bulk densities, their potential use in development of gastroretentive dosages are highly plausible.

The results suggest that the Kollicoat® IR and Kollicoat® Protect work as good binders, but the binding properties of Kollicoat® Protect outperforms that of Kollicoat® IR in direct compression and in wet granulation matrice (Fig. 3, Table I). Such a significant difference between the two is due to the strong binding properties of PVA in Kollicoat® Protect. Our study further shows that Kollicoat® IR tablets floated for over 4 hr, while those of Kollicoat® Protect floated for over 24 hr. Furthermore, Kollicoat® IR tablets prepared either by DC or wet granulation floated immediately (t_{lag} 0), attributed due to highly hydrophilicity of the polymer, whereas, Kollicoat® Protect tablets prepared by DC floated in approx. 60 sec or less (t_{lag} <1 min), while others showed different t_{lag} depending upon the excipients used in the granulation.

In general, lower t_{lag} are required for immediate floatation to prevent migration of the dosages to the duodenum and lower intestine. Granulation improved the hardness of Kollicoat® Protect more significantly over Kollicoat® IR (Table 1), and also significantly increased the t_{lag} (Fig. 5). Thus, Kollicoat® Protect with its lower lag time, superb free flowing characteristics, low bulk density, low specific gravity (gastric fluid <1.004 g/cm³) provides immediate floatation and buoyancy. In addition, this non-effervescent excipient provides a stability advantage over traditional effervescent systems containing sodium bicarbonate and an organic acid for generation of carbon dioxide.

Conclusions

The data suggests that PVA-PEG copolymers can be used as dry binders and as matrices for FDDS. The study further demonstrates that Kollicoat® Protect outperformed Kollicoat® IR. The low bulk density, and micro-porosity provide buoyancy to the tablets with extended floating characteristics, and thus alleviating the instability associated with the gas-generating components requiring acids and bases.

Further studies are underway to assess the extended release from the gastroretentive dosages of Kollicoat® Protect.

References

1. Arora, A.; Ali, J.; Ahuja, A; Khar, P. K.; and Baboota, S.; AAPS PharmSciTech, 2005, 6, 372-390.

2. (a) Sheth, P. R, US Patent 4,167,558 (1979); (b) Lee, P., US Patent 4,340,491 (1982); (c) Shell, J. W.; and Louie-Helm, J., US Patent 5,972,389 (1999); (c) Illum, L.; and Ping, H., US Patent 6,207,197 (2001); (d) Fukuda, M; Peppas, N. A.; and McGinity, J. W., J. Contr. Release, 2006, 115, 121-129..

3. Machida, Y.; Inouye, K.; Tokumura, T.; Iwata, M; and Nagai, T., Drug Design & Delivery, 1989, 4, 155-161.

4. Hassan, C. M.; and Peppas, N. A., J. Applied Poly. Sci., 2000, 76, 2075-2079

5. Scheider, M; and Bussat, P., US Patent 2002, 6403057.

6. (a) Kollicoat® IR, BASF Technical Bulletin (b) Kollicoat® Protect, BASF Technical Bulletin

7. Quadir, A. Unpublished work