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# Successful Binding of Peroxide-Sensitive APIs



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## The Growing Importance of Peroxides in Formulation

Peroxide-induced API degradation is getting more attention in the industry. For instance, in September 2010, the FDA was concerned about the influence of peroxide impurities on povidones and crospovidones imported from the Far East into the US-market. The agency was much concerned that this might lead to sub-potent drugs, in case such a product found its way into formulations.

There are various possibilities how organic peroxides can influence the stability of API in formulations. As a result, there are many reasons why it is important to reduce peroxide exposure in a formulation: new APIs, low-dosage formulations, product life cycle management, and cost efficiency. Newly developed chemical entities are often highly sensitive, and additionally the low dosing of such products is in need of new binders to reduce peroxide levels.

In the case of life-cycle management, there is growing pressure on a pharmaceutical company to position themselves with a new, competitive and differentiating dosage form. There is growing pressure on pharmaceutical companies to position themselves with new, competitive and differentiating dosage forms. This increases the need for new excipients that enable those new dosage forms, and reduced peroxide exposure is one element to it.

With regard to cost efficiency, the trend toward generics puts pressure on the market to reduce cost. By avoiding API degradation, an optimum of API amount formulated can be achieved.

## Reducing Oxygen Exposure: The PeroXeal™ Solution

**Figure 1** shows a simple composition of a tablet: drug, filler, binder, disintegrant, and in many cases, coating. Looking at these components, two can be identified as typically prone to forming peroxides: the binder and the disintegrant. Controlling peroxide formation is twofold; either reduce the oxygen exposure or influence the cycle by which peroxides

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are formed.

BASF has developed a way to reduce oxygen exposure by innovating its PVP packaging significantly, reducing oxygen permeation - PeroXeal™ avoids oxygen exposure of polymer throughout the packaged shelf life. PeroXeal™ features an EvOH inner liner material and is nitrogen flushed heat-sealed, making it oxygen impermeable.

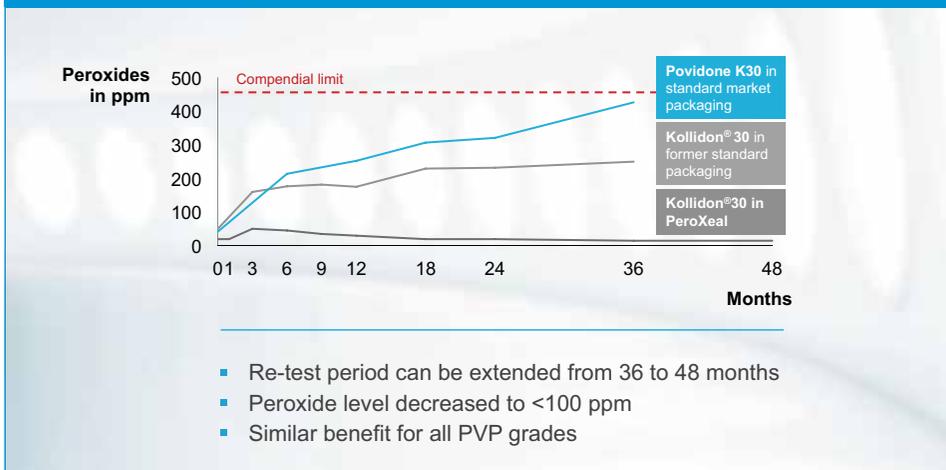
**Figure 2** compares peroxide levels of regular Povidone, Kollidon and peroxeal packed Kollidon, measured in a long-term stability study. The blue line represents Povidone K30 in standard market packaging. The central line is Kollidon® 30 in former BASF standard packaging, and the bottom line represents Kollidon®30 in PeroXeal™. Results show that even if there is some remaining oxygen in the Peroxeal™ packaging, the level declines over time due to the degradation of the peroxides in the packaging, allowing a shelf life increase from 36 to 48 months. With the introduction of PeroXeal™, BASF eliminated peroxide exposure up to the point where the package is opened **Figure 3**.

In addition to BASF's PeroXeal™ Kollidons, there is a Kollidon 30LP (low peroxide) that is spiked with an anti-oxidant - this extends the period of low exposure as the anti-oxidant takes up formed peroxides. Consequently the protection of the active ingredient is further extended.

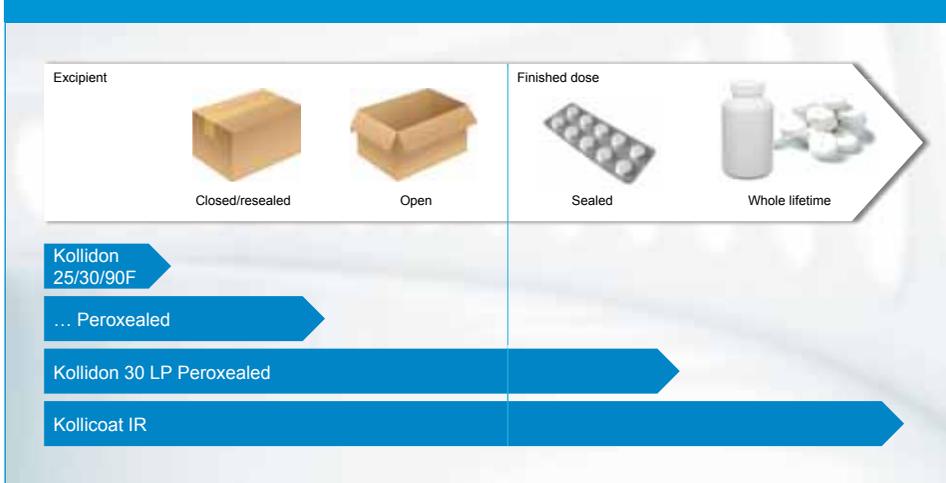
**Figure 1: Binders and disintegrants are often source of peroxides**



**Figure 2: Long term stability data shows that PeroXeal™ significantly reduces peroxide formation**



**Figure 3: Peroxide protection along product lifecycle**



However, there is a certain limitation to that antioxidant effect: as soon as it is used up, the API is likely to be subject to regular peroxide exposure and degradation.

Finally, as presented in **Figure 3**, Kollicoat IR, originally introduced as an instant-release coating, is also a very potent binder. Making Kollicoat IR extra special is the fact that it does not exhibit peroxide formation at all. Thus, peroxide exposure remains practically inexistent for the API, even throughout the lifetime of the finished dosage form.

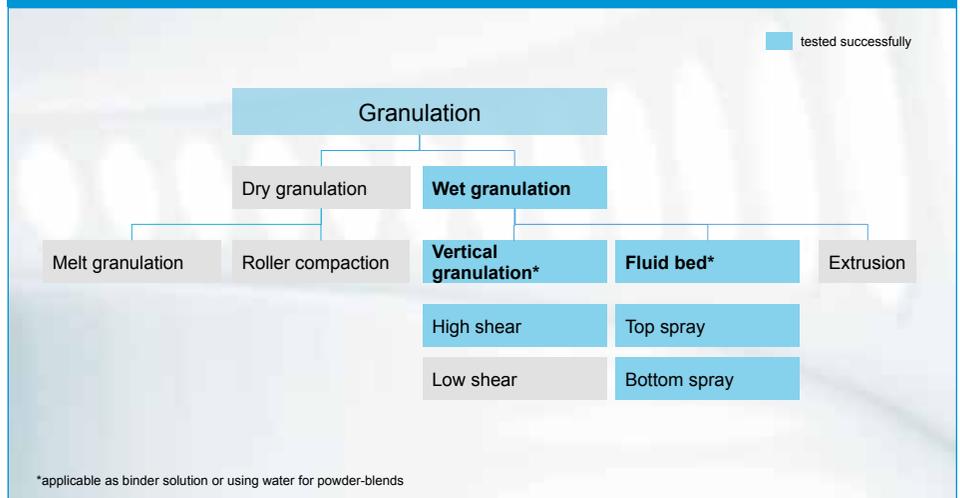
**A New Option**

Kollicoat IR is a grafted copolymer, with polyethylene glycol as backbone. To this polyethylene glycol, the polyvinyl alcohol is attached. The overall molecule weight roughly is 45,000 AMU. **Figure 4** highlights the processing technologies in which Kollicoat IR has already been successfully tested.

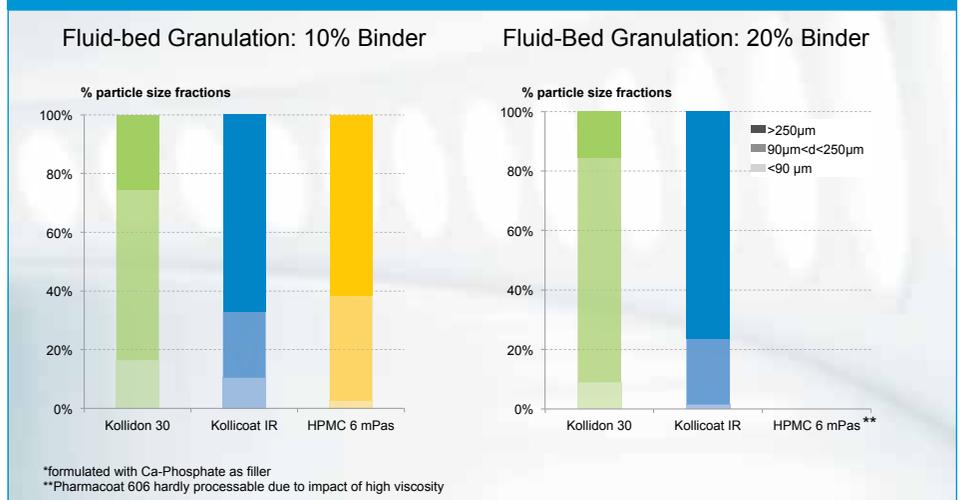
To demonstrate Kollicoat IR in a fluidized bed granulation set up, BASF used a simple propranolol formulation with calcium phosphate as filler and 10 and 20% of wet binder, respectively. Kollicoat IR was compared to HPMC and Kollidon 30. With 20% binder, Kollicoat IR leads to considerably higher granulation success **Figure 5**.

When the tablets were compressed, tensile strength was compared. With 10% binder, Kollicoat IR showed outstanding tensile strength at low compression force. At 20% binder, the advantages of

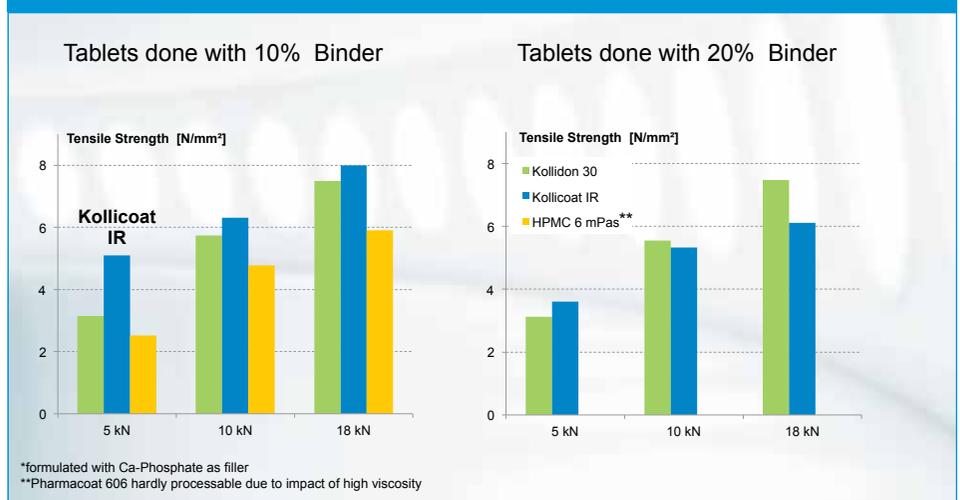
**Figure 4: Kollicoat IR binding processability proven in fluid bed and high shear granulation**



**Figure 5: With 20% binder, Kollicoat IR leads to significantly higher granulation success\***



**Figure 6: Kollicoat IR shows outstanding tensile strength at low compression force\***



the Kollidon 30 are evident, but nevertheless, the Kollicoat IR is at least as good as the standard grade binder **Figure 6**.

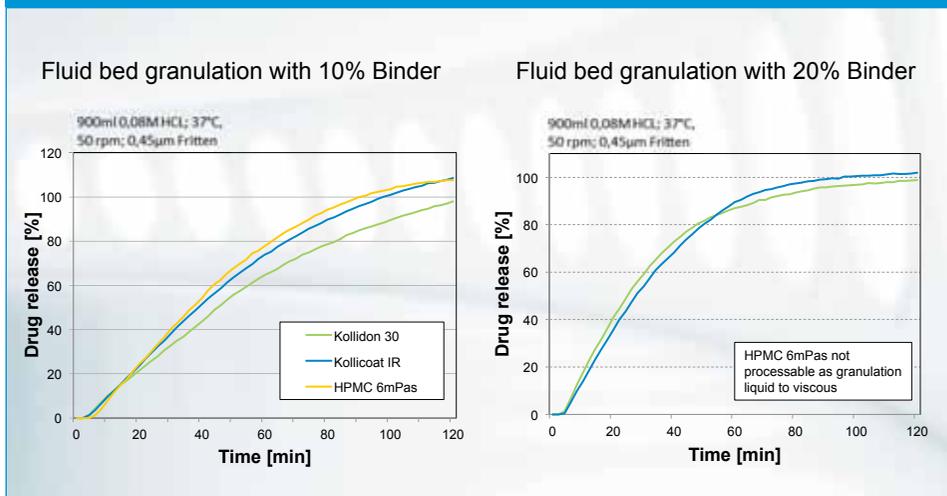
When putting the tablets through a dissolution test, dissolution was not delayed or negatively influenced by the type of binders. Kollicoat IR released the API as good as the Kollidons **Figure 7**.

In a high shear granulation test, the binder content was set to 5%. The composition is once again propranolol in a calcium phosphate filler system, and the entire mix was granulated with an aqueous binder solution. Here, Kollicoat IR performs comparable to the Kollidons. In terms of the tensile strength, the Kollicoat IR presented acceptable tensile strength **Figure 8**.

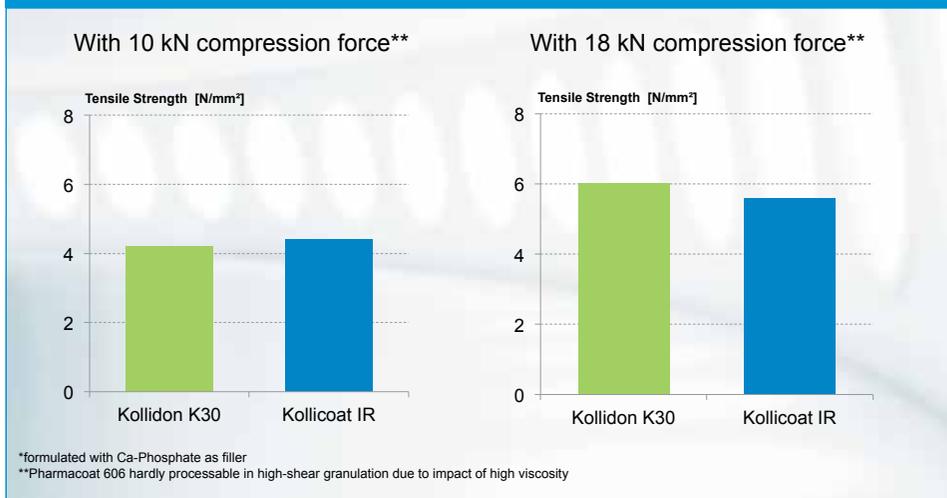
Now take a look at the peroxide levels **Figure 9**. Even at these extreme conditions, there is basically no peroxide formation.

To show the non-existing degradation effect of Kollicoat IR in a formation with an API, BASF did not use any components that can form peroxides, except the binder. Raloxifene was chosen and formulated in with calcium phosphate. At a 6% binder level, several binders were used as shown in **Figure 10**. After a short period of time and at accelerated storage conditions, the two binders without protection or an antioxidant system formed degradation. Here, Kollicoat IR shows its advantage over standard grades of binders coming out of the povidone range.

**Figure 7: API release is as fast as with Kollidon 30**



**Figure 8: In high-shear granulation, Kollicoat IR performs comparable to the Kollidons\***



**Figure 9: Kollicoat IR does not show peroxide buildup! Measured following Ph.Eur. 8th ed 2.5.5**

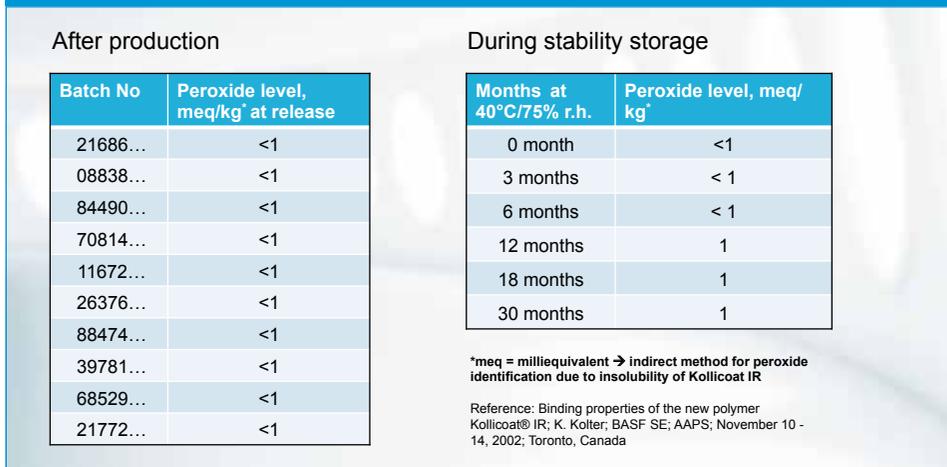


Figure 10: No degradation products of Raloxifene traceable when Kollicoat IR is used

Formulation		6% binder	
Sr. No	Ingredients	mg/tab	% content
1	Raloxifene hydrochloride	60	30
2	Binder	12	6
3	DCP (Calipharma A)	122	61
4	Aerosil 200	4	2
5	Magnesium Stearate	2	1
<b>Total</b>		<b>200</b>	<b>100</b>

Degradation products of Raloxifene (60mg/tablet) in stability (Raloxifene-N-oxide)

Binder type/-quantity	Unit	Initial	1 month	3 month	6 month
Kollicoat IR - 6%	%	0	0	0	0
Kollidon 30 LP - 6%		0	0	0	0
Povidone K29/32 - 6%		0	0.02	0.02	0.02
KD 30 (in PE): sample 1&2 - 6%		0	0.02	0.02	0.02

Figure 11: Summary – Kollicoat IR combines the best of PVP and cellulose derivatives in one binder

	Kollicoat IR	Kollidon 25 / 30	Kollidon 90F	Cellulose derivatives	Native starch
Viscosity*	low	low	high	medium/high	high
Binding power	high	high	very high	medium	medium
Processing window	wide	wide	wide	small	small
Pre-processing	no	no	no	no	yes
Organic solvents	no	yes	yes	yes	no
Peroxides	no	low/medium	low/medium	no	no

\*in aqueous solution

\*\*due to Peroxexal packaging / antioxidant in Kollidon 30 LP

### Summary

Kollicoat IR has the unique combination of high binding power, low viscosity, easy processing and no peroxide formation, making it a superior choice when faced with formulating a peroxide-sensitive API **Figure 11**.