Expert Opinion

1. Introduction
2. Background and characterization
3. Types of Kollicoat IR
4. Registered tablets coated with Kollicoat IR
5. Preclinical studies of Kollicoat IR
6. Application of Kollicoat IR in solid dispersion
7. Application of spray drying in the preparation of drug/ Kollicoat IR solid dispersions
8. Use of Kollicoat IR in controlled release tablet coating
9. Conclusions
10. Expert opinion

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Technology evaluation: Kollicoat IR

Ehab A Fouad, Mahmoud El-Badry, Steven H Neau, Fars K Alanazi & Ibrahim A Alsarra[†]

[†]*King Saud University, College of Pharmacy, Department of Pharmaceutics, Riyadh, Saudi Arabia*

Introduction: Developments in industrial pharmacy are often linked to the discovery of pharmaceutical excipients. Although recently introduced as a material for immediate release coatings, Kollicoat IR® already has other applications.

Areas covered: In this review, the different properties and pharmaceutical applications of Kollicoat IR as an excipient are discussed. In the first part, the chemical structure and the physicochemical characteristics are examined. The second part is a presentation of the available Kollicoat IR products followed by a brief overview of the preclinical studies completed for its use as an instant release coating material.

Expert opinion: Although the polymer was intended as an immediate release coating material for tablets, grafting PEG with polyvinyl alcohol to form this polymer provides physicochemical properties that lead to ever-broadening applications. Understanding its properties can lead to the development of a new use for Kollicoat IR. The addition of Kollicoat IR to an ethylcellulose or polyvinyl acetate tablet coat was successful at modifying the drug release rate. Designing a successful controlled release coat simply requires acknowledgment of the drug release mechanism from the mixture of polymers that includes Kollicoat IR. Moreover, the interaction between Kollicoat IR and poorly soluble drugs produces fast-dissolving solid dispersions prepared using hot stage extrusion, spray drying, or freeze drying.

Keywords: controlled release coating, Kollicoat IR, preclinical studies, registered products, solid dispersion, spray drying

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1. Introduction

Kollicoat IR® (**Figure 1**) is a poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG). It was introduced to pharmaceutical research as an excipient and a film coating polymer by BASF Chemical Co. (Ludwigshafen, Germany) with the aim of producing an immediate release dosage form [1,2]. **Figure 2** shows a scanning electron microscopic image of Kollicoat IR particles.

The polymer is composed of ~ 75% PVA units and 25% PEG units, with PEG providing the backbone of the branched copolymer and PVA forming the branches. It has been reported that Kollicoat IR has a molecular mass of ~ 45,000 Da [2].

2. Background and characterization

According to DeMerlis and Schoneker [1], orally administered PVA is relatively harmless. The safety of PVA is mainly determined based on the low acute oral toxicity of PVA, with LD_{50} values in the range 15 – 20 g/kg [2]. Orally administered PVA is poorly absorbed from the gastrointestinal tract [3]; it does not accumulate in the body when administered orally [4]. PVA is neither mutagenic nor clastogenic [5]. Adverse effects of orally administered PVA in male and female rats

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Article highlights.

- Orally administered PVA is poorly absorbed from the gastrointestinal tract; it does not accumulate in the body when administered orally. PVA is neither mutagenic nor clastogenic.
- Kollicoat IR®, a copolymer of PVA and PEG, forms clear, colorless films that are flexible and that dissolve rapidly in water.
- Preclinical studies have examined the differences between the components of the Kollicoat IR copolymer, Kollicoat IR itself, and other types of polymers in pharmaceutical processes.
- Kollicoat IR can act as a carrier in solid dispersions that provide the amorphous form of drugs to enhance dissolution rate and bioavailability.
- Kollicoat IR microparticles can be prepared by spray drying, freeze drying, or hot stage extrusion.
- Controlled release coatings for tablets or pellets can be achieved using a film coat with low permeability that contains Kollicoat IR as a pore former.
- Recommendations are made for further application of Kollicoat IR.

This box summarizes key points contained in the article.

were not reported even at the highest dose of 5000 mg/kg (body weight) per day in the 90-day dietary study and 5000 mg/kg (body weight) per day in the two-generation reproduction study [5]. A critical evaluation of the existing information on PVA supports its safety for use as a coating agent for pharmaceutical and dietary supplement products [1]. The use of PVA as a film coating agent has been suggested previously [2]. Although its rapid solubility in cold water renders it economical for use in current aqueous film coating processes, its practical use is hindered by the tackiness of the hydrated polymer.

The addition of plasticizer to the film will affect its mechanical properties through the increase in film elongation that decreases the elastic modulus and tensile strength values [3-5]. In addition, plasticizer may promote an increase in the viscoelastic behavior of the polymer. Usually, the addition of PEG as a plasticizer is intended to reduce the brittle nature of the film because a brittle polymer encourages a coat to crack. PEG with a nominal molecular mass of 1000, or preferably 3000, has been found useful for this purpose [3]. The ability of PEG to reduce the glass transition temperature of the film-forming polymer makes the polymer less brittle in the dried film [3-5]. Inclusion of PEG, however, would be expected to result in a tackier coating fluid. Accordingly, adding PEG to PVA, which is already tacky when hydrated, would be expected to result in a coating fluid that is unacceptably tacky [2].

Grafting ethylene glycol and vinyl alcohol produced the copolymer Kollicoat IR (**Figure 1**), which is potentially useful in a hydrophilic tablet coat or in the preparation of solid dispersions. The polymer is composed of 75% PVA units grafted onto PEG units, which comprise the remaining 25%. Its solubility is 40% w/w in aqueous systems and 25% w/w in a 1:1 ethanol/water mixture [4]. The solubility in nonpolar solvents is low; it can only be dispersed in these solvents [4]. This hydrophilic polymer is slightly surface-active and semicrystalline [2], with the PEG component acting as an internal plasticizer. Kollicoat IR forms clear, colorless films that are flexible and that dissolve rapidly in water. Kollicoat IR films are not tacky, unlike PVA and PEG films or their mixed polymer films. Kollicoat IR films have a high pigment binding capacity and can be printed readily. In comparison with films of cellulose derivatives, films of Kollicoat IR have a much higher elongation at break [3].

The Fourier transform infrared (FTIR) spectrum of Kollicoat IR and that of PVA and of PEG are presented in **Figure 3**. In comparison with the spectrum for PVA, the spectrum for Kollicoat IR shows enhanced reduction in per cent transmission at ~ 2900, 1460, 1100, 960 and 850 cm^{-1}. On examination of the spectrum for PEG, it is clear that these examples of enhanced reduction in percent transmission for Kollicoat IR are due to the presence of the PEG backbone in Kollicoat IR.

Using modulated differential scanning calorimetry to characterize Kollicoat IR as received from the manufacturer, BASF [4] found that melting starts at ~ 170°C with a peak at 212°C, while another melting endotherm was visible at 15°C. There were two glass transition temperatures evident in the thermogram; the first was at -57°C and the second at 45°C. These results indicate that the PEG portion acts as an internal plasticizer, as suggested by the manufacturer [2], rather than solely as a separate entity, as the PVA glass transition is reported to take place at 92°C [6] and its melt at 228°C [7]. The melting endotherms confirm that both the PEG and PVA parts of Kollicoat IR are at least semicrystalline in nature. After spray drying, Kollicoat IR was more amorphous than the starting material if the inlet temperature was kept below 170°C [8].

Testing Kollicoat IR with three different plasticizers, namely PEG 400, propylene glycol and diethyl phthalate, at 10 and 30% w/w levels indicated that, depending on the type and the concentration of the plasticizer, a preference for one of the two amorphous phases (PEG or PVA fractions) can occur, which may lead to different physical stability profiles, depending on which amorphous phase is involved [8].

Using hot-melt extrusion, Kollicoat IR oxidation takes place, and it becomes yellow or even brown colored. Increases in the crystallinity of the PVA fraction of the material are believed to be a result of the effects of both temperature and shear forces. The PEG fraction remains unaffected. The use of ultra-fast chip calorimetry experiments showed that a cooling rate of 3000°C/s was necessary to make PEG/PVA completely amorphous, indicating that applying forced cooling after extrusion in order to make the extrudates completely amorphous is essentially impossible [8].

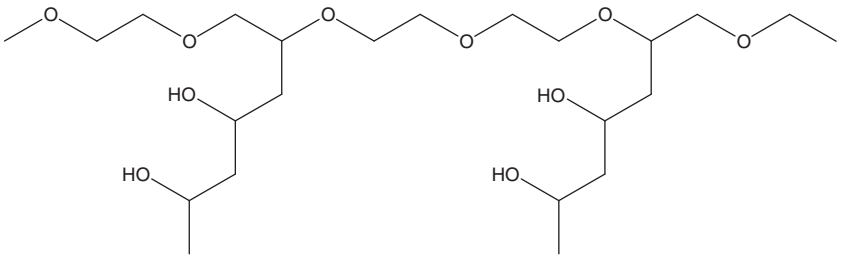

Figure 1. Kollicoat IR® chemical structure (ChemOffice 2004, version 8, CambridgeSoft Corp., Cambridge, USA).

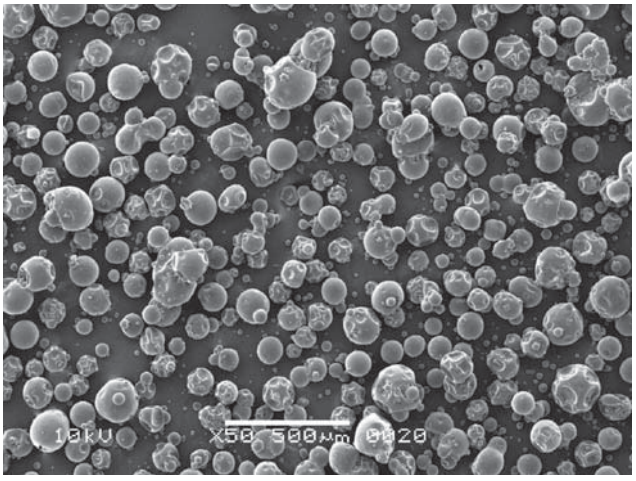

Figure 2. Scanning electron microscopic image of Kollicoat IR® microparticles.

3. Types of Kollicoat IR

1) *Kollicoat IR.* The poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer consists of 75% PVA units and 25% PEG units. It also has 0.3% of colloidal silicon dioxide to improve its flow properties. It is used in instant release coating of tablets, pellets and particulate matter. It is also applicable as a binder and in binding solutions for wet granulation.
2) *Kollicoat IR White.* This consists of 45 – 74% of Kollicoat IR, 5 – 10% of Kollidon® VA 64 (copovidone, BASF), 10 – 20% of titanium dioxide, 10 – 20% of kaolin and 1 – 5% of sodium lauryl sulfate. It is utilized in spray-dried ready-to-use instant release coatings with white pigment.
3) *Kollicoat IR White II.* This is a spray-agglomerated form of Kollicoat IR white. It is mainly designated as a ready-to-use instant release coating miscible with a variety of colors or pigments.
4) *Kollicoat Protect.* This consists of 55 – 65% of Kollicoat IR, 35 – 45% of polyvinyl alcohol and 0.1 – 0.3% silicon dioxide. It is applied in ready-to-use taste masking or as a moisture barrier in combination with various colors or pigments [9].

4. Registered tablets coated with Kollicoat IR

To the authors' knowledge, two dosage forms have been registered.

1) Germany's Federal Institute for Drugs and Medical Products has registered a 1000 mg metformin formulation (Registration No. 59553.00.00) encapsulated in Kollicoat IR as an instant release film [10].
2) Ibuprofen tablets coated with Kollicoat IR have been described in an abbreviated application (ANDA 75 – 661) in the US [11].

5. Preclinical studies of Kollicoat IR

The published preclinical studies were carried out by BASF. They were investigating the properties of Kollicoat IR in comparison with various additives that serve as similar excipients (**Table 1**). Using a 20% Kollicoat IR dispersion to make a cast film with a thickness of ~ 100 µm, Kolter *et al.* [5] studied the elongation at break and the tensile strength at different humidities, the dissolution rate, and the tack in comparison with Pharmacoat® 603 and 606 (Hydroxypropyl methylcellulose 3 and 6 mPa s viscosity grades). They found that the PVA component provides good film-forming properties and the PEG component acts as an internal plasticizer leading to flexibility (elongation at break: 105%). The internal plasticizer cannot migrate during storage because it is covalently bound in the molecule. The flexibility is thus maintained because rearrangement of the molecules to a high level of order (crystallization) is prohibited [12]. Humidity in the range 30 – 75% relative humidity (RH) has practically no influence on the mechanical properties of Kollicoat IR films. There was no difference in the dissolution rate in 0.08 N HCl and phosphate buffer pH 6.8. Low tack values were measured even at high relative humidity [12].

As the ability to spray a coating fluid is strongly influenced by its viscosity, the viscosities of dispersions of the instant release polymers Kollicoat IR, Pharmacoat 603 and Pharmacoat 606 were compared at a polymer concentration

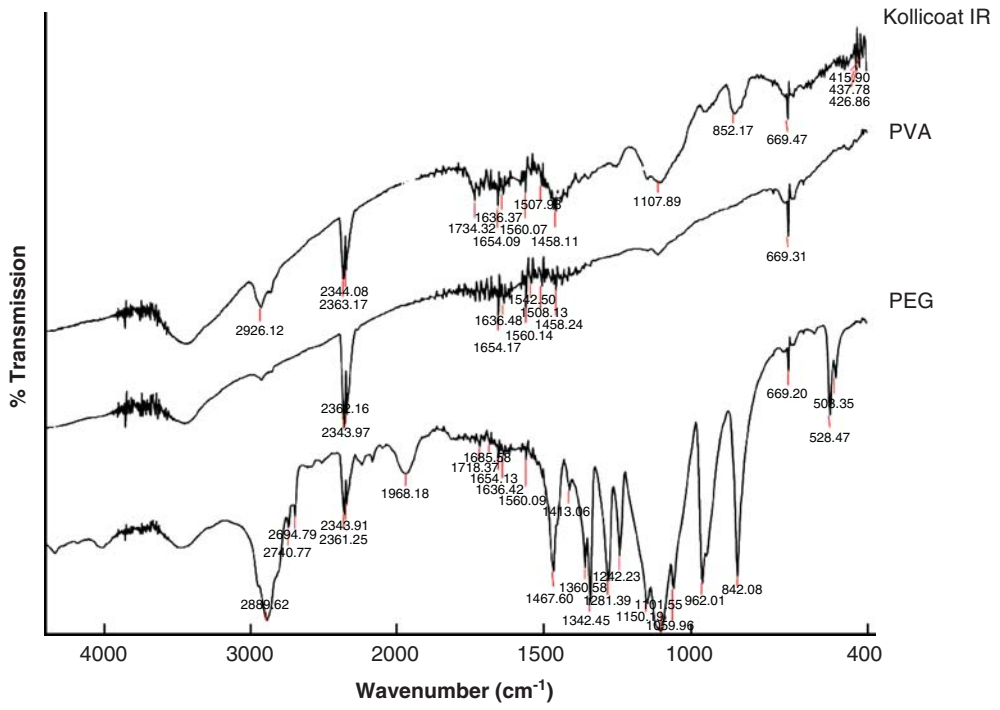

Figure 3. Fourier transform infrared spectra of Kollicoat IR, PVA and PEG.

Table 1. Summary of Kollicoat IR® preclinical studies carried out by BASF.

Type of study	Publication year	Ref.
Physicochemical characterization	2002	[5]
Innovation in instant release film coatings	2002	[13]
Scale-up of an instant release film-coating process	2002	[14]
Binding properties	2003	[15]
Viscosity and pigment-binding capacity	2004	[16]
Protection of light-sensitive active ingredients	2005	[17]
Comparison of the coating properties of instant release film coatings	2007	[18]

of 20%. Kollicoat IR gave a much lower viscosity than the cellulose derivatives, thus allowing it to be sprayed even at higher concentrations.

The elongation at break of Kollicoat IR films (105%) far exceeds that of the Pharmacoat cellulose derivatives (4 and 17%) and should therefore prevent any cracking. There is no need to add any plasticizer to Kollicoat IR films. From the physicochemical data, a Kollicoat IR coating fluid containing 20.8% polymer and 11.7% pigments with a viscosity of 193 mPa s could be applied easily using a horizontal pan coater, whereas this was not possible with Pharmacoat 606. With higher solids content in the coating fluid, coating times can be shortened. Also, coatings with Kollicoat IR are stable in storage even at high humidity [13].

Kolter [14] investigated the film coating of 40 mg propranolol HCl biconvex tablets with the aim of scaling up film coating [14]. The spraying rate of the Kollicoat fluid, the inlet air volume and the inlet air temperature were varied. The dissolution rate, disintegration time, hardness and appearance of the coated tablets were assessed. He found that the coating process with Kollicoat IR can easily be scaled up from laboratory to production scale, yet the coated tablet properties remain unchanged. The coating process was extremely fast, even with a 250 kg batch. In scaling up, the inlet air temperature, relative spraying rate and relative inlet air volume should be kept constant.

Kollicoat IR, Kollidon® VA 64 and hydroxypropyl methylcellulose (HPMC) 3 mPa s revealed excellent binding properties in both mixer and fluid bed wet granulation methods. The formation of granules is promoted by the excellent film-forming properties of the polymers. In addition, Kollicoat IR demonstrated excellent agglomeration activity. Compression of Kollicoat IR granules of ascorbic acid resulted in tablets with low ejection forces, high hardness and short disintegration times when compared with tablets manufactured with Kollidon VA 64 or HPMC 3 mPa s [15].

Kolter [16] evaluated the influence of pigments on the viscosity of Kollicoat IR dispersions and the mechanical

properties of the films, in comparison to dispersions and films with Pharmacoat 603 and 606. In addition, he studied the possible influence of temperature elevation and shear stress on the viscosity of Kollicoat IR solutions. It was found that the viscosity of Kollicoat IR dispersions can be markedly reduced by increasing the temperature; shearing has no influence on the viscosity. The use of Kollicoat IR results in much lower viscosities than observed with the HPMC products. Addition of talc increases the viscosity of the HPMC dispersions more than that of Kollicoat IR dispersions. Kollicoat IR has a much greater pigment binding capacity than do the HPMC products.

To study the protection of light-sensitive active ingredients, Ziegler and Kolter [17] measured the transmission spectrum of light protection amber glass, cast Kollicoat IR films and Kollicoat IR-film-coated nifedipine tablets with different coloring agents from BASF, namely, iron oxide (Sicovit® Red 30, E 172), erythrosine aluminum lake (E 127) and indigotine aluminum lake (E 132). Light protection properties of Kollicoat IR films pigmented with red iron oxide are comparable to those of amber-colored light-protecting glass containers. The films fulfil the specification of the European Pharmacopoeia for light transmission for colored light-protecting glass containers.

Cech and Kolter [18] compared the coating properties of Kollicoat IR with those of HPMC by keeping the weight gain and the batch size constant. They found that the processing time can be reduced up to 50% compared with HPMC-based coating material owing to the higher solids content of Kollicoat IR White. Kollicoat IR White allows a broad range of process parameters in dry or wet processes. The ability to run a coating process at temperatures below room temperature provides a distinct advantage with temperature-sensitive drugs. The wide range of settings leads to a robust and reproducible coating process. Transfer either to other coater types or to larger scales is quite simple when using Kollicoat IR White.

In general, it can be assumed that a lower viscosity of the polymer dispersion will facilitate the preparation of the film coating fluid and the hydrophilicity of the polymer will lower the risk of lumps in the dispersion, such that less air will be incorporated. Kollicoat IR offers a better surface quality to the coated tablets, higher solids content in the dispersion, a shorter processing time and a lower processing cost.

Hydrophilic polymers may form a matrix with hydrophobic drugs to separate drug particles effectively, improve wetting and enhance the dissolution rate. There is a definite need to explore new carrier materials that are compatible with most drugs [19,20]. Solid dispersions of BCS class II drugs with a polymer such as Kollicoat IR as the carrier will act to enhance their dissolution rate. Although Kollicoat IR was developed for use as a hydrophilic film-forming polymer, it has an advantage that, as a non-ionic polymer, its solubility is pH-independent. Its surface activity and low viscosity when it is dissolved in water are advantageous to its use in solid dispersions.

6. Application of Kollicoat IR in solid dispersion

Solid dispersions are among the most successful strategies to improve the dissolution rate of poorly soluble drugs. These dispersions can be defined as mixtures of poorly water-soluble drug in a carrier where drug dissolution or its release profile is driven by the carrier properties.

The most common solid dispersions present the drug molecularly dispersed within an amorphous carrier [21], and polymeric carriers in particular have accomplished this. Povidone [22-29], PEGs [30-34] and polymethacrylates [35-37] are among the polymers used for this purpose. Other polymers of natural origin include cellulose derivatives [37-42] and starch derivatives [40,41].

A solid dispersion can be classified according to the molecular interaction of drug and carrier as a solid solution, a solid suspension, or a mixture of the two [22,25]. In a solid solution, drug and polymer are totally miscible, generating a homogeneous molecular dispersion [22]. This type of solid dispersion is homogeneous on a molecular level and, therefore, only one phase is present [22].

A solid suspension occurs when the drug has limited solubility in the carrier or an extremely high melting point [43]. On a molecular level, this dispersion is composed of two phases, one rich in carrier and one rich in drug. When a drug is both dissolved and suspended as small particles in the carrier, a heterogeneous structure is obtained with mixed properties of a solid solution and a solid suspension [22,44]. A water-soluble carrier will provide separation of drug particles, improve wettability and dispersibility of the drug, solubilize the drug, and perhaps produce an amorphous form of the drug and its carrier [45,46].

Using hot stage extrusion, Janssens *et al.* [47] prepared solid dispersions of itraconazole and Kollicoat IR with different ratios of drug to carrier. The dissolution profile shows that the drug dissolves rapidly and remains solubilized; because of the formation of amorphous phases, the drug can dissolve quickly along with Kollicoat IR. The high aqueous solubility of Kollicoat IR and the resulting low viscosity of the aqueous medium enhanced the dissolution process.

7. Application of spray drying in the preparation of drug/Kollicoat IR solid dispersions

Among the techniques to prepare a solid dispersion, spray drying has been widely utilized in both the pharmaceutical and food industries because of its suitability as a production method. It has the ability to produce spherical and size-controlled particles and simultaneously to improve the dissolution properties. However, this technique is not appropriate for thermolabile or oxidizable actives, such as biological drugs, because it requires heat and the rapid velocity of high volumes of air.

Using a two-nozzle spray-drying apparatus, Janssens *et al.* [48] prepared spray-dried microparticles by dissolving itraconazole in 50/50 v/v dichloromethane/ethanol, but Kollicoat IR was dissolved in 50/50 v/v ethanol/water. Modulated differential scanning calorimetry, X-ray powder diffraction and dissolution studies provided no evidence of the collision of droplets and consequent molecular level mixing. In particular, the thermograms revealed only features of the pure Kollicoat IR and pure itraconazole. Consequently, the dissolution rate of these solid dispersions was poor.

A turbid system was obtained when the two solutions were prepared separately and then mixed together before spray drying with a one-nozzle apparatus [48]. As Kollicoat IR solubility is not affected by pH, Janssens *et al.* acidified the turbid mixture with HCl to allow complete dissolution of itraconazole. The mixture proved to be metastable and formed two layers on standing. Nevertheless, with immediate use of the acidified mixture, the itraconazole was dispersed on a molecular level in the Kollicoat IR microparticles, and each solid dispersion prepared was amorphous. Increasing the Kollicoat IR content led to an increase in the dissolution of itraconazole. **Table 2** summarizes the published Kollicoat solid dispersion research articles.

El-Badry *et al.* [49] used a 2:1 v/v hydroalcoholic system to dissolve completely omeprazole–Kollicoat IR mixtures to study the effects of different drug–Kollicoat IR ratios on the dissolution rate of omeprazole from microparticles prepared using spray- and freeze-drying techniques. Physicochemical properties of the microparticles were investigated using differential scanning calorimetry, powder X-ray diffraction and scanning electron microscopy and revealed the transformation of omeprazole from crystalline to amorphous. Spray drying produced a solid solution containing 80% Kollicoat IR that allowed complete omeprazole dissolution within 15 min, with a dissolution rate about nine times the rate of the physical mixture. The freeze-dried product allowed dissolution at a rate seven times that of the physical mixture (**Figure 4**). These microparticles were incorporated into enteric coated capsules as well as into a suppository dosage form [50].

8. Use of Kollicoat IR in controlled release tablet coating

Oral controlled release dosage forms have high patient compliance and receive great attention in the pharmaceutical industry as a convenient means to control drug delivery. Controlled release of drug from tablets or pellets is typically achieved using a film coat where a slower release is achieved with lower permeability through the coat. Nevertheless, the polymer film should still allow release of the drug at a rate that meets therapeutic need. In practice, this compromise can be difficult to achieve. Physical parameters such as membrane permeability, thickness and surface area can be modified to obtain the desired release rate.

Ethylcellulose is a good film-forming agent, non-toxic, non-allergenic and a non-irritant [51]. The use of aqueous dispersions of ethylcellulose offers the advantages of minimized toxicity and environmental concerns in comparison with the use of organic solutions, as well as shorter processing times owing to the higher solids content in the dispersion than in a solution. However, long-term consistent drug release patterns might be difficult to claim if the film is not fully coalesced. Further gradual coalescence during storage results in decreased drug permeability and, thus, decreased release rates [52,53]. It was found that the addition of small amounts of Kollicoat IR to an aqueous ethylcellulose dispersion can significantly improve film formation and/or curing, allowing for long-term stable drug release profiles, even on storage under stress conditions for 6 months [54,55].

Siepmann and co-workers [54,55] tested the effect of 2.5 – 10% Kollicoat IR in an ethylcellulose film. The addition of small amounts of Kollicoat IR significantly increased the rate and extent of water uptake, irrespective of the pH of the release medium. The permeability of the films increased significantly with an increase in Kollicoat IR content, probably owing to dissolution of at least part of the Kollicoat IR found in the coat [54]. Owing to the increase in length of the diffusion pathways, the relative drug release rate decreases with an increase in the coating level. However, higher coating levels are often desirable because the effects of slight variations in the final coating thickness are less pronounced than observed with thin polymer coatings. Thus, desired drug release rates from ethylcellulose-coated dosage forms can be adjusted effectively and easily by adding only small amounts of Kollicoat IR and by varying the coating level over a reasonable range. Unlike HPMC, the presence of this PVA-PEG graft copolymer does not cause flocculation of the coating dispersion [54].

The presence of small amounts of Kollicoat IR in aqueous ethylcellulose dispersions effectively improved film formation during coating and curing, and essentially eliminates further polymer particle coalescence during long-term storage. The improved film formation during coating and curing might be attributed to the ability of Kollicoat IR to hold water during film formation. Water acts as a plasticizer for ethylcellulose and, thus, increases the mobility of the macromolecules and facilitates polymer particle fusion [55].

Muschert and co-workers [56,57] studied the release of different drugs, namely, diltiazem HCl, paracetamol, metoprolol succinate, metoprolol tartrate and theophylline, from sugar cores or microcrystalline cellulose cores that were coated with an aqueous dispersion of ethylcellulose with Kollicoat IR. They found that the addition of small amounts of Kollicoat IR to the ethylcellulose coating fluid allowed controlled drug release over 8 – 12 h, irrespective of the type of drug and composition of the pellet core. Drug release was found to be controlled by diffusion through the intact polymeric membranes, irrespective of the drug solubility and type of core formulation [57].

Table 2. Summary of published Kollicoat solid dispersion research articles.

Drug	Method	Solvent system	Ref.
Itraconazole	Hot stage extrusion	None necessary	[47]
Itraconazole	Spray drying	50/50 v/v dichloromethane:ethanol for the drug 50/50 v/v water:ethanol for Kollicoat	[48]
Omeprazole	Spray drying and freeze drying	Ethanol/water	[49,50]

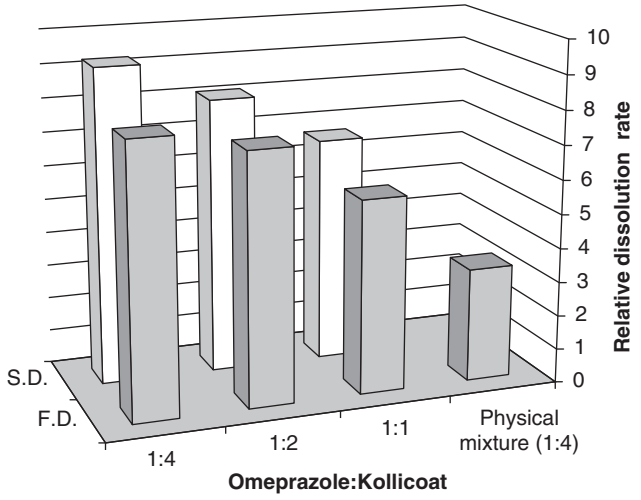

Figure 4. Effect of Kollicoat concentration on the relative dissolution rate of omeprazole spray-dried (S.D.) and freeze-dried (F.D.) microparticles in comparison with the physical mixture.

In another study, Strübing *et al.* [58] used proton NMR (^{1}HNMR) spectra to quantify the leaching of Kollicoat IR from an isolated film. A fast decrease in Kollicoat IR concentration was observed for the first 30 and 60 min for Kollicoat® SR/Kollicoat IR coats at 8:2 and 9:1 ratios, respectively, followed by a slower release over several hours. An increase in Kollicoat IR in the film is reflected by a faster initial loss in its concentration.

Ensslin and co-workers [59,60] used energy-dispersive X-ray analysis along with nuclear magnetic resonance and electron paramagnetic resonance spectroscopies to study the sigmoidal release of chlorpheniramine maleate from pellets coated with polyvinyl acetate (PVAc)/Kollicoat IR. The polymer blend ratio and the film thickness were each found to have a major influence on the drug release and dissolution rate, in stark contrast to the insignificance of the plasticizer concentration.

It is well known that a PVAc/Kollicoat IR film coat starts to swell after exposure to water [61]. This swelling can minimize the effect of imperfections in the film coat by reducing the holes, craters and clefts found in the dried coat. Ensslin *et al.* [62] reported that, even after piercing the PVAc/Kollicoat IR coat with a 26-gauge needle, the damaged pellets yielded a drug release profile comparable to that of undamaged coated pellets. However, when the coat was sliced with a razor blade and the blade entered the core pellets, the self-repair mechanism of the PVAc/Kollicoat IR film coat was unable to compensate fully for this damage.

Muschert *et al.* [63] found that drug release is primarily controlled by diffusion through the intact polymeric membranes, irrespective of the type of core or release medium. Assuming that the drug is molecularly dispersed within the core and that the surface area of the film coat is large compared with its thickness, edge effects are negligible and the mathematical analysis of drug release can be restricted to one dimension. Under these conditions, the release kinetics can be described by Fick's second law of diffusion in a plane sheet.

In another study, the mechanism of floating and drug release behavior of propranolol HCl-containing tablets coated with Kollicoat SR 30 D and Kollicoat IR at two ratios, 9:1 and 8.5:1.5, was investigated [64]. The purpose of such a dosage form is to provide retention of the device in the stomach so that drug is released to act locally. The core tablets incorporated compressible Kollidon SR as a low-density excipient and sodium bicarbonate to generate carbon dioxide on exposure to the acidic gastric fluid. The lag time before floating was related to the coating level linearly for the 8.5:1.5 SR/IR (sustained release/instant release) ratio coats and almost exponentially for the 9:1 ratio coats. The floating delivery devices were able to deliver drug with nearly zero-order kinetics over a 24 h period following the lag time. An increase in the Kollicoat IR content of the coat reduced the lag time and increased the drug release rate. The authors explained that the higher Kollicoat IR content resulted in a more permeable coat for hydrochloric acid penetration and a more flexible coat that can be more easily expanded by the carbon dioxide gas formation, resulting in a device that can float earlier.

9. Conclusions

This review article sheds light on the newly developed hydrophilic polymer Kollicoat IR. Although the polymer was intended as an instant release coating material for tablets, it has been discovered that grafting PEG with PVA to form this polymer provides physicochemical properties that lead to ever-broadening applications. The addition of Kollicoat IR to the controlled release film of ethylcellulose or PVAc was highly successful at modifying the drug release rate. Moreover, the interaction between Kollicoat IR and poorly soluble drugs produces fast dissolving solid

dispersions prepared using a hot stage extruder, spray drying, or freeze drying.

10. Expert opinion

Developing a new pharmaceutical excipient that can have a wide range of applications is a challenge. Ideally, a newly developed polymer should have broad use in different dosage forms, prove to be safe, and be easily and inexpensively manufactured. Although indeed rare, Kollicoat IR has proved to be such a polymer. Its unionizable chemical structure has provided distinct advantages for consistent drug release profiles that are not dependent on the pH of the release medium.

Kollicoat IR was initially intended to coat tablets where immediate drug release was desired. The use of this polymer in the preparation of solid dispersions certainly expanded its applications. Using spray drying as a means to obtain solid dispersions provided a powder product of uniform particle size and homogeneous drug distribution, except with the use of two fluids of dramatically different polarities and a two-nozzle spray-drying system. Under those circumstances, the probability of collision and successful miscibility of the unlike droplets was low. Spray drying a nanosuspension of the drug in the polymer solution can result in coated particles that should disperse and dissolve rapidly in gastrointestinal fluids. Decreasing the evaporating temperature to 170°C will result in the distinct advantage that the amorphous form of Kollicoat IR is obtained. Fast drying of the droplets will often lead to rapid precipitation of the dissolved drug in its amorphous form, which, along with amorphous Kollicoat IR, will dissolve easily and rapidly in a dissolution medium. The use of freeze drying as a successful alternative technique for preparation of solid dispersions with Kollicoat IR expands the application of Kollicoat IR to its use with thermolabile drugs. However, the use of Kollicoat IR in hot stage extrusion will depend on the time of operation, the screw rate and the temperature, as well as the percentage of drug used. In this case, the resultant solid dispersion will be a mixture of amorphous and crystalline drug and perhaps also a mixture of amorphous and crystalline Kollicoat IR. Further study on this use of Kollicoat IR might be necessary to convince those in the pharmaceutical industry of its ready application in hot stage extrusion.

Applying Kollicoat IR as a component in a controlled release film expanded its applications even further. At issue is the distribution of Kollicoat IR in the matrix polymer and the potential for Kollicoat IR to be partially or completely entangled in the matrix polymer network. In the release medium, the unentangled fraction can be released quickly, followed by slow release of the entangled fraction. Rapid release of unentangled Kollicoat IR will open up low tortuosity pathways for dissolved drug diffusion and will result in an initial rapid release of drug from pores of limited size and number. Slow release of entangled Kollicoat IR will eventually open up new pores and provide larger pores that will increase the drug release rate at later times. This could result in a biphasic release profile or possibly the more desirable zero-order release profile. If a biphasic mechanism of pore formation is undesirable, the choice of matrix polymer might prove to be critical. Nevertheless, the release mechanism for drugs from such a system can thus vary widely depending on the matrix polymer used in the controlled release coat, the level of Kollicoat IR in the coat, and the coating level. Reports on the further utilization of Kollicoat IR in controlled release coating of tablets, pellets and granules are expected.

The use of Kollicoat IR in a suppository dosage form is recommended because it will of course have a positive influence on the bioavailability of BCS class II drugs. Utilization of Kollicoat IR in externally applied films that have an occlusive backing should also show promise because the ability of Kollicoat IR to take up water will allow the film to swell and then diffusion pathways will become less tortuous. Thus, drug leaching during storage can be minimized, but drug release will be encouraged after application owing to the entrapment of sweat by the occlusive backing, which results in swollen Kollicoat IR. Its use in mucoadhesive films should also be explored because the abundance of water should allow the Kollicoat IR to swell substantially and yet not diffuse away owing to the intimate contact with the mucus membrane.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Ehab A Fouad[1,2], Mahmoud El-Badry[1,2], Steven H Neau[3], Fars K Alanazi[1,4] & Ibrahim A Alsarra[†1,5]
[†]Author for correspondence
[1]Professor,
King Saud University,
College of Pharmacy,
Department of Pharmaceutics, PO Box 2457,
Riyadh 11451,
Saudi Arabia
Tel: +966 1 4677504; Fax: +966 1 4676363;
E-mail: ialsarra@ksu.edu.sa
[2]Assiut University,
Faculty of Pharmacy,
Department of Pharmaceutics,
71526 Assiut, Egypt
[3]University of the Sciences in Philadelphia,
Philadelphia College of Pharmacy,
Department of Pharmaceutical Sciences,
600 South 43rd Street,
Philadelphia, PA 19104, USA
[4]King Saud University,
College of Pharmacy,
Kayyali Chair for Pharmaceutical Industry,
Riyadh, Saudi Arabia
[5]King Saud University,
Center of Excellence in Biotechnology Research,
PO Box 2460, Riyadh 11451,
Saudi Arabia