ORIGINAL ARTICLE

Delivering drug-polymer complex via quick dissolving film: A step towards the development of an appropriate pediatric formulation

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Lack of suitable prednisolone formulations for treatment of asthma could limit treatment compliance in pediatric population and hence the aim of this study was to develop prednisolone-polymer complexes with enhanced solubility and to incorporate this complex into orally disintegrating films to enable rapid drug delivery. The prednisolone-polymeric complexes were prepared using solvent evaporation and freeze drying techniques with a drug-polymer ratio of 1:1 using hydroxypropyl β-cyclodextrin (HP β-CD), hydroxypropyl methylcellulose 4 cps, and polyvinylpyrrolidone K-30 as polymeric carriers and the parameters such as an aqueous solubility, dissolution profile, and solid-state characterization using differential scanning calorimetry (DSC) of the complexes determined. The optimized complex was then incorporated into films prepared using solvent casting technique and the weight variation, thickness, solid-state characterization, *in vitro* disintegration and dissolution profiles of the films were then determined. The highest prednisolone solubility was seen with the prednisolone-HP β-CD complex prepared by freeze drying (1.82 mg/mL) followed by the same complex prepared by solvent evaporation (1.70 mg/mL). The solubility's were significantly higher compared to prednisolone powder (0.2 mg/mL) ($P < 0.05$). DSC analysis of complexes revealed a reduction in area of the endothermic peak indicating the presence of amorphous drug while in comparison, the DSC analysis of films did not show endothermic peak showing complete absence of crystalline drug. The film was thin, uniform in weight and thickness, showing rapid disintegration of 55 s with almost complete drug release within 3 min. The study revealed the incorporated drug-polymer complex have maintained the amorphous state and enabled rapid drug release.

Key words: *Freeze drying, pediatric drug delivery, prednisolone, quick dissolving thin film, solid dispersions, solvent evaporation*

INTRODUCTION

Asthma is a common chronic inflammatory condition of the airways with around 5.4 million people in the UK receiving treatment. This accounts for approximately 1 in 12 adults and 1 in 11 children.[1] The causes of asthma are not completely understood, but the disease can be characterized by airflow limitation, airway hyper-responsiveness to stimuli and inflammation of the bronchi.[2] Prednisolone, a glucocorticoid, is a drug commonly used for acute asthma, but unlike the other drugs recommended for asthma, is only available as a tablet for oral administration. When prednisolone is taken as a tablet, the drug is absorbed from the intestine,[3] with peak plasma concentrations being achieved within 1-2 h.[4] This delayed onset of action is highly undesirable, particularly when prompt use of prednisolone in acute asthma can help reduce morbidity and the need for hospital care.[5]

The success of a drug's formulation is not only dependent on pharmacotherapy, but also on compliance.[6] Compliance to treatment is very important, with some of the main causes being around awkwardness around taking the medication, the severity of the asthma causing difficulty in taking the medication, inconvenience caused by having to take numerous medications[7] and intolerable side effects caused by ingredients in the formulation (e.g., vomiting).[8] It has been reported that

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there is a shortage of formulations available for pediatric use, with Pharmacists often having to adapt formulations, so they are more suitable,[6] as swallowing tablets can be a big issue in children,[9] which ultimately results in patient receiving inappropriate treatment and results in therapeutic failure.

Liquid formulations such as solutions or suspensions are easy to administer and the dosage can be easily measured if required but conversely, issues such as short-term stability, bulky transport, uses of preservatives and anti-oxidants to avoid microbial growth on multiple dosing are the problems associated with such formulations. Oro-dispersible formulations are gaining popularities owing to have distinct advantages over conventional formulations. Such as no water required, compact, long-term stability compared to liquid products, and also manipulation of dose according to weight of children can be possible.[10,11] Considerable difficulties are, however, likely to be encountered when relatively high tablet strengths are required to be administered. In addition, the increased complexity in development and cost of manufacturing such as use of freeze drying techniques and specialized blister packaging system limits it's applicability in cost effective disease management system. Looking further to overcome these issues, rapidly disintegrating thin film dosage forms are evolved as an alternate choice of dosage forms, which does not need complex production facilities and still offer competitive advantages such as improved patient compliance, no water needed for administration, accurate dosing and enhanced stability with cost effective disease management.[12] Dose adjustment can be possible by cutting the films into appropriate size as required hence it will give flexibility in dosing across different children without altering physical or chemical properties of dosage forms.

Poor solubility of drug is the key factor need to overcome to be able to deliver the drug via film type dosage form. This highlights the two aims of the study. The first is to improve the water solubility of prednisolone, with the second being to deliver this prepared drug polymer complex via film dosage forms. Prednisolone is a poorly soluble drug with a reported solubility of 0.2 mg/mL.[13] Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients[14] and it provides a means of reducing particle size to a nearly molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. In particular, polymers such as polyethylene glycols, low molecular weight hydroxypropyl methylcellulose (HPMC), hydroxypropyl β-cyclodextrin (HP β-CD) and polyvinylpyrrolidone (PVP) have been used extensively as carriers for SDs because of their hydrophilic nature.[15] Although solvent evaporation method is one of the more widely used methods to prepare SD, freeze-drying is a less frequently exploited technique. Freeze-drying offers a number of advantages due to the minimal thermal stress applied during the preparation. Only limited attempt have been to directly compare SDs prepared by spray-drying and freeze-drying method.[16] However, only few studies have incorporated SD into target formulation for further evaluation for its feasibility. As such, the aim of the current study was to formulate and characterize the prednisolone-polymer complex and to deliver it using quick dissolving film as technological platform aimed at pediatric drug delivery system.

MATERIALS AND METHODS

Materials

Prednisolone, polyvinyl alcohol (PVA, Mowiol 4-88) and PVP K-30 were purchased from Sigma Aldrich Ltd (Dorset, UK). Pharmacoat 904 (HPMC) 4 cps was received as a gift sample from R.Q. Unwin (Herts, UK). Cavasol W7 HP Pharma (HP β-CD) was received as a gift sample from International Speciality Products (ISP) Corporation (Covington, USA). All other chemicals and reagents used in the study were of analytical grade and purchased from Fisher Scientific Ltd (Loughborough, UK).

Preparation of drug polymer complexes

Solvent evaporation method

Three polymers (HP β-CD and HPMC 4 cps, PVP K-30) were individually used to prepare prednisolone SDs at a drug to the polymer ratio of 1:1 using the solvent evaporation technique [Table 1]. Briefly, 0.5 g of prednisolone and 0.5 g of polymer were accurately weighed and dissolved in 50:50 mixture of dichloromethane and ethanol mixture to get clear solution via manual stirring. The drug-polymer solutions were transferred on to a petri dish where they were left overnight to allow evaporation of the solvents. The samples were placed in the vacuum oven at 40°C for 45 min to ensure complete evaporation of solvents. The dried mass was scrapped and passes through 355 μ sieve to get uniform size particles and packaged in glass vials until further use.

Freeze drying method

Three polymers (HP β-CD and HPMC 4 cps, PVP K-30) were individually used to prepare prednisolone SDs at a drug to polymer ratio of 1:1 using ultra-rapid freezing technology [Table 1]. Briefly, 0.5 g of prednisolone and 0.5 g of each polymer were accurately weighed and dissolved

Table 1: Composition of solid dispersion complexes

Batch no.	Manufacturing method	Polymer*
PS1	Solvent evaporation	HP β-CD
PS2	Solvent evaporation	HPMC 4 cps
PS3	Solvent evaporation	PVP K-30
PF1	Freeze drying	HP β-CD
PF2	Freeze drying	HPMC 4 cps
PF3	Freeze drying	PVP K-30

*Drug to polymer ratio is kept constant at 1:1 HP β-CD: Hydroxypropyl β-cyclodextrin, HPMC: Hydroxypropyl methylcellulose, PVP K-30: Polyvinylpyrolidone K30

or dispersed in purified water with manual stirring and freeze-dried after filling into the plastic container in a lyophilizer. During operation, the freeze-drier was maintained as: −45°C for 1 h, followed by −30°C for 3 h, followed by −10°C for 3 h and finally at 20°C for 12 h with constant compression pressure of 0.5 Torr. After complete drying, the vials were taken out, and the dried products were scraped from the vials. The formulations were powdered, passed through 355 μ sieve and packaged in glass vials until further use.

Preparation of film containing optimized drug-polymer complex

The films containing optimized drug-polymer complex were prepared by solvent casting technique. Briefly, PVA (1 g) was dissolved into a previously boiled water (40°C) under constant stirring followed by addition of maltodextrin (0.25 g) as a pore former and glycerin (0.2 g) as a plasticizer and finally at the end, required amount (10 mg of complex equivalent to 5 mg of prednisolone, total of 0.250 g for 25 films) of drug-polymer complex was added to this solution with continuous stirring on magnetic stirrer. The resultant clear solution was poured over 10 cm × 10 cm of Teflon plate (Cowie technology, Middlesbrough, UK) and left overnight at room temperature to dry. After drying, the films were checked for any imperfection or bubbling via visual observation and peeled off from the cast and cut into a size of 2 cm × 2 cm to contain 5 mg of prednisolone per film section.

Characterisation of SD complexes and films

Saturation solubility study

Plain drug and SD complexes in excess quantity were placed in separate glass vials containing 10 mL of artificial saliva (1.688 g of sodium chloride, 2.4 g of potassium chloride, 0.386 g of calcium chloride dihydrate, 0.222 g of magnesium chloride hexahydrate and 0.684 g of dibasic potassium phosphate in 2.0 L of purified water) and the samples were placed on a magnetic plate with water bath with controlled heating at 37°C (RCT Basic IKA Larbortechnik, Germany) at 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through 0.45 μm membrane filter and the filtrates were diluted appropriately using artificial saliva and analysed using double beam Ultraviolet (UV) spectrophotometer (T80 UV/Vis Double Beam Spectrometer, PG Instruments Ltd, UK) at 248 nm. The amount of drugs solubilized was calculated using developed calibration curve in artificial saliva with R^2 of 0.998.

Differential scanning calorimetry

The Differential scanning calorimetry (DSC) measurements were performed using a DSC Q2000 (TA Instrument, UK). The instrument was calibrated with Indium before the start of the experiments. Samples weighing approximately 5 mg were cut, sealed in aluminium pans, and analyzed in an atmosphere of nitrogen at flow rate of 25 mL/min. A temperature range of 0-200°C was used, and the heating rate was 10°C/min. DSC measurements of drug-free films, pure prednisolone and excipients were also performed for comparison purposes.

Content of drug in complexes and film

The drug-polymer complexes (20 mg containing 10 mg of drug) and equivalent films were accurately weighed and transferred to 100 mL of artificial saliva followed by sonication to ensure complete extraction of drug. The solution was then filtered using 0.45 μm membrane filters and diluted appropriately and analyzed using double beam UV spectrophotometer at 248 nm.

Physical characterization of films

The thicknesses of 10 random films were measured using a micrometer (Silverline, Somerset, UK) and an average thickness with standard deviation was calculated. A total of 20 random films were weighed individually and average weight with standard deviation was calculated.

In vitro disintegration test of films

The 2 cm × 2 cm size of film was put in 10 mL of artificial saliva pH 5.7 in a glass vial and the time at which the films disintegrated (visual observation) was noted ($n = 3$).[17]

In vitro dissolution study

The dissolution study was performed in 10 mL of artificial saliva as a dissolution medium in a glass vial. The solution was continuously stirred in a glass vial with use of a magnetic flea at 400 rpm on magnetic stirrer. The pure drug, drug-polymer complexes and a film (2 cm × 2 cm) equivalent to 5 mg of prednisolone were placed in separate vials and at a predetermined time interval 1 mL of sample was withdrawn and replaced with fresh medium. After appropriate dilution, the samples were filtered and analyzed using double beam UV spectrophotometer at 248 nm. The cumulative percentage drug release was calculated and plotted against time ($n = 3$).

RESULTS AND DISCUSSION

Prednisolone being poorly soluble drug may pose a significant hurdle to the formulation scientists in developing orally disintegrating drug delivery system especially when drug required to be deliver in a matter of seconds and subsequent appearance of drug in plasma is warranted as quickly as possible to relieve the symptoms of acute asthmatic attack without compromising the compliance and concordance in pediatric population, which is now a center point of discussion among industries and several regulatory bodies across the world.

The polymers chosen to prepare SD such as HP β-CD, HPMC and PVP K-30, were all widely used to enhance the solubility of poorly soluble drugs using different methods[18-20] at different ratio and looking at the literature, the drug to polymer ration proved to be most efficient in majority of the cases is 1:1 hence it was decided to start with this ratio to screen the optimum polymer suitable to enhance the prednisolone solubility.

Solvent evaporation and freeze drying methods were explored to increase the solubility and dissolution rate of prednisolone using three different polymers to evaluate the influence of manufacturing method as well as type of polymer on solubility and dissolution enhancement of prednisolone by keeping the drug to the polymer ratio constant throughout the study.

The solubility results in artificial saliva for pure drug, SD complexes prepared using different polymers via solvent evaporation and freeze drying were depicted as Table 2. The artificial saliva was used as a medium to carry out solubility and dissolution study to simulate the *in vivo* situation of formulation when placed upon a tongue or cheek. The results revealed that the solubility of the drug was influenced via both the method and the type of polymer used to manufacture the complexes.

The highest prednisolone solubility was seen with the prednisolone-HP β-CD complex prepared by freeze drying (1.82 mg/mL, Table 2, Batch PF1)followed by the same complex prepared by solvent evaporation (1.70 mg/mL, Table 2, Batch PS1). These solubility results were significantly higher compared to prednisolone powder (0.2 mg/mL) ($P < 0.05$). The complexes prepared using HPMC (PF2 and PS2) and PVP (PF3 and PS3) did increase the solubility compared to pure drug, but the increase was not that significant when compared to complexes prepared using HP β-CD. For example, in case of HP β-CD (PS1 and PF1), the solubility was increased 7.6 and 8.1 fold compared to solubility of pure prednisolone, while in case of PVP K-30 (PS3 and PF3), the fold increase in solubility was 1.35 and 1.30 only when complexes prepared using solvent evaporation and freeze drying, respectively. So the rank order in term of solubility enhancement of prednisolone is HP β-CD followed by HPMC and PVP independent of method used for preparing such complexes. Similar observation was also reported in literature where inclusion of poorly soluble drug with cyclodextrin has increased solubility by 10 fold in case of imatinib,[21] 11 fold in case of furosemide[22] while just 4.5 fold increase in solubility was observed for bupivacaine,[23] so it seems to be dependent on the molecular interaction of cyclodextrin and drug.

Table 2: Solubility of prednisolone as pure drug and from solid dispersion complexes

Batch no.	Solubility (mg/mL) (mean±SD, *n*=3)	Fold increase in solubility
Prednisolone	0.225±0.01	-
PS1	1.700±0.07	7.55
PS2	0.563±0.12	2.50
PS3	0.305±0.09	1.35
PF1	1.820±0.14	8.08
PF2	0.542±0.05	2.40
PF3	0.294±0.02	1.30

To investigate the mechanism behind increased solubility, all the prepared complexes, films as well as pure drugs were analyzed using DSC to check possible conversion of crystalline to amorphous nature. DSC analysis of SD complexes [Figures 1 and 2] revealed a reduction in area of the endothermic peak indicating the presence of amorphous drug. The pure drug has showed endothermic peak at the melting point (250°C) while the curve for the dispersion prepared using either freeze drying or solvent evaporation did show reduction in the peak area of the endothermic curve with a little shift of melting point (238°C), which proved homogenous distribution of drug in the polymer backbone and is present as amorphous form.

In comparison, the DSC analysis of films did not show endothermic peak showing complete absence of crystalline drug. This may be due to presence of PVA and maltodextrin in film as well as the solvent casting method used to manufacture film. Solvent casting methods involve dissolution/dispersion of drug-polymer complexes and other

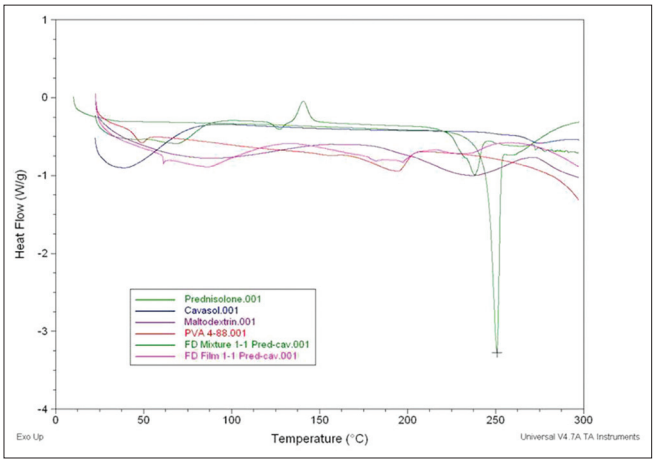

Figure 1: Differential scanning calorimetry curve of prednisolone film with solid dispersion complex prepared using freeze drying (Cavasol is tradename for hydroxypropyl β-cyclodextrin)

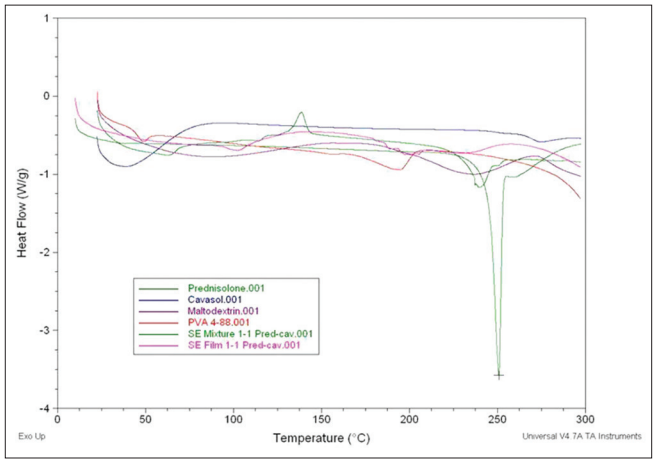

Figure 2: Differential scanning calorimetry curve of prednisolone film with solid dispersion complex prepared using solvent evaporation (Cavasol is tradename for hydroxypropyl β-cyclodextrin)

required excipients followed by removal of solvent via drying, which resembles solvent evaporation process. The presence of PVA and maltodextrin, which are hydrophilic in nature may have further enhanced the homogenous distribution of drug within the polymer along with HP β-CD and resulted into complete drug-polymer miscibility and hence may have prevented the drug from crystallizing out on drying, which is often observed after drying of the thin films.

The films produced were translucent, colorless, thin and flexible with no obvious imperfections. The prepared films were evaluated for their physicochemical properties such as uniformity of weight, drug content and thickness of the films. The uniformity of content showed that the drug was uniformly distributed throughout the films and was within pharmacopoeial limits (85-115% of the labeled claim) for drug content.[24] The average thickness of the films was found to be 130 ± 10 μm (n = 10) while the average weight of the films ranged from 68.59 ± 5.52 mg (n = 20). The disintegration test revealed rapid disintegration of 55 ± 5 s (n = 6). The rapid disintegration was observed due to presence of highly hydrophilic polymer used to manufacture the film as well as the presence of maltodextrin, which act as rapidly dissolving pore former, which may have accelerated the disintegration process via formation of holes within the films on contact with aqueous medium.[25,26]

An *in vitro* drug dissolution test was performed for pure prednisolone powder, SD complexes, film in a small volume of artificial saliva to mimic the *in vivo* situation of formulation. There is no as such any official guidance is available to carry out the dissolution of rapidly disintegrating films meant to be placed within the mouth for quick dissolution. Figure 3 showed comparative dissolution profile of prednisolone from pure powder against the SD complexes (PS1 and PF1). The significantly rapid release of prednisolone was observed from SD complexes prepared using both the method compared to pure prednisolone powder ($P < 0.05$). The rapid release may be due to increased solubility of drug in complexes along with partial amortization of drug resulted in faster dissolution compared to untreated drug. The slower dissolution of prednisolone from powder was observed may be due to crystalline nature of drug and poor wettability of drug itself, which can delay the wetting of powder and subsequent dissolution. The plateau was observed in dissolution profile of prednisolone powder, which may be due to attainment of the maximum saturation solubility which have further retarded the dissolution of un-dissolved drug and potentially have contributed towards constant release profile. In comparison, in case of complexes plateau was not observed in dissolution profile and its obvious due to the fact that drug is partially present in amorphous form as well as the presence of hydrophilic polymer and rapidly dissolving pore former have accelerated the wetting and resulted in rapid and complete release in a small volume, which is warranted in real scenario when formulation placed upon tongue or beneath the cheek for rapid dissolution. Similar observation was also reported where the dissolution rate of meloxicam was higher from SD complex incorporated into a buccal patch by solvent evaporation technique compared to pure meloxicam.[27]

Figure 4 showed comparative dissolution of prednisolone from pure powder, SD complex and the film prepared using optimized complex. The SD complex was incorporated into a film to deliver the drug via oral mucosa. The prednisolone-polymer complex has retained the rapidly dissolving characteristics even after its incorporation into a film which shows that films has demonstrate capability to deliver the drug efficiently despite being small volume of saliva used in the dissolution test to simulate the *in vivo* condition. The dissolution of prednisolone was comparable between the SD complex and the film and extent of dissolution was significantly higher from both SD complex and the film compared to untreated powder ($P < 0.05$). This is again due to presence of drug in amorphous state in the film as evident from DSC profile [Figures 2 and 3] and the process involved in preparation of film as described earlier. Solvent casting method used for manufacturing of film resembles the solvent

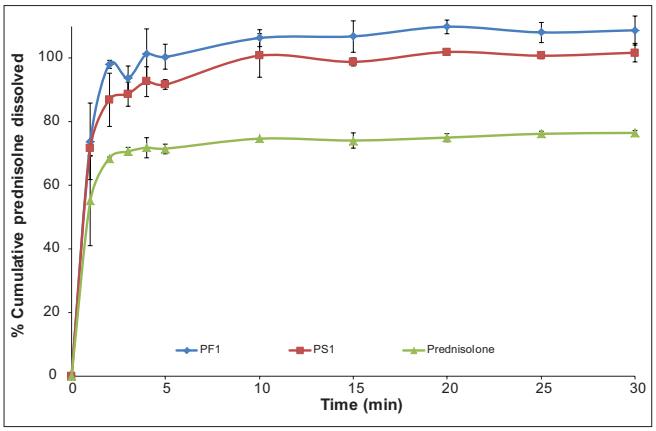

Figure 3: Comparative dissolution profile of prednisolone from pure powder and the solid dispersion complexes (PS1 and PF1) (n = 3)

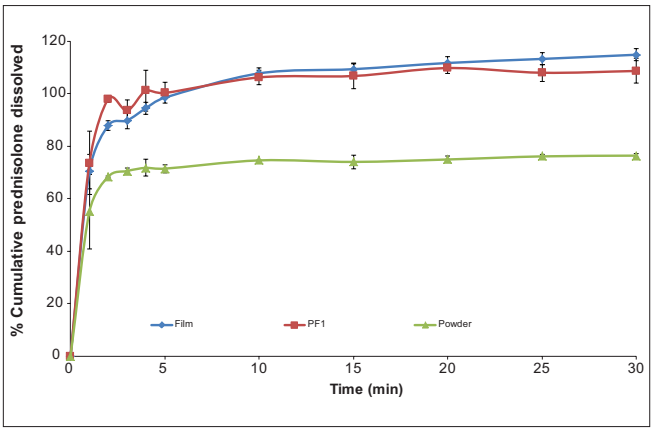

Figure 4: Comparative dissolution profile of prednisolone from pure powder, freeze dried complex (PF1) and film (n = 3)

evaporation process known to increase the solubility of poorly soluble drug. Furthermore, in addition to method, the presence of highly hydrophilic polymer PVA along with rapidly dissolving pore former maltodextrin has enabled the rapid disintegration and subsequent dissolution of prednisolone from film formulation. Several hydrophilic polymers are reported in literature to enhance the solubilization capacity of cyclodextrin complexes.[28]

CONCLUSION

The study revealed that solubility and dissolution rate of prednisolone was enhanced in presence of HP β-CD compared to other polymeric carriers and drug itself. The study also showed that the incorporated drug-polymer complex have maintained the amorphous state of drug and enabled rapid drug release. Hence it is possible to deliver the poorly soluble drug in a form of a drug-polymer complex via an appropriate selection of excipients and the manufacturing method for both SD complex and the film formulation.

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