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Review article

A review on new technology for modified drug release: Accudep technology

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Key words: Accudep technology, controlled-release, immediate-release, electrostatic deposition, pharmaceutical active powder.

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Abstract

Accudep technology is a new advanced technique ideally suited to pharmaceutical dosage form manufacturing. Accudep technology is a single continuous automated process which is being applied to a range of product areas including intermediate-release dosage forms, super generic products and novel controlled-release formulations. The technology is a highly-controlled electrostatic deposition process. The key steps in the process are attachment of film substrate to a patterned receiving module, controlled deposition of pure pharmaceutical powder onto the patterned regions on the substrate film, dose measurement, lamination to second film and processing into final dosage form. The goal is to identify highly flexible delivery designs that will accommodate many drugs of diverse physicochemical characteristics, dose ranges and facilitate engineering of immediate as well as controlled-release of the pharmaceutical active powder. The system design differs from currently marketed controlled-release products in that it avoids the conventional pharmaceutical processes such as–mixing, blending, granulation, drying, sizing and compression. Instead, the proposed system utilizes active drug moieties as pure active ingredient, and achieves controlled-release through the use of polymeric film of various release characteristics. It provides several benefits to the pharmaceutical industry including lower manufacturing costs, more precise dosing, a cleaner manufacturing environment and fewer waste materials. Hence Accudep technology can be used to prepare low dose, potent drug with known content uniformity and stable immediate release dosage forms.

Introduction

Oral drug delivery system is the most widely used and convenient option as the oral route provides maximum effective surface area among all drug delivery systems for administration of drug. The allurement of this drug delivery system is due to its awareness of toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets and capsules. Modified-release drug delivery is designed to overcome the fluctuations caused by conventional dosage forms [1]. Modified-release is used to describe the dosage form in which the drug release pattern is based on time, course and location that are designed to accomplish therapeutic objectives not offered by conventional dosage forms [2]. Modified-release drug delivery system has been designed to extent the drug release for several hours (by mixing the drug with release retardant materials). Modified-release dosage form provides reduction in dosing frequency, dose reduction, less side effects and better therapeutic activity and enhancement of bioavailability [3].

Modified-release drug delivery system has been classified into:

1) Controlled release
   i. Sustained release
   ii. Extended release
   iii. Prolonged release
2) Delayed release Controlled release [1]

Controlled - release drug delivery systems are dosage forms from which the drug is released by a pre-determined rate which is based on a desired therapeutic concentration and the drug's pharmacokinetic characteristics [4].

Sustained release drug delivery systems include any drug delivery system that achieves slow release of drug over an extended period of time [5].

Extended release drug delivery systems are defined as the dosage forms that allows a reduction in dosing frequency from that necessitated by a conventional

dosage form, such as a solution or an immediate-release dosage form [2].

Prolonged release drug delivery systems are defined as the dosage forms that prolong the therapeutic blood or tissue levels of the drug for an extended period of time [6].

Delayed release drug delivery system is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like GI pH [2].
The ideal drug delivery system should be inert, biocompatible, mechanically strong, capable of achieving high drug loading, safe from accidental release , simple to administer and remove, and easy to fabricate and sterilize. The goal of this system is to achieve a delivery profile that would yield a high blood level of drug over a long period of time [4].

Advantages of Modified Release:

1. Reduced dosing frequency
2. Dose reduction.
3. Improved patient compliance.
4. Constant level of drug concentration in blood plasma.
5. Reduced toxicity due to overdose.
6. Reduces the fluctuation of peak valley concentration.
7. Uniform release of drug.
8. Reduce side effects.
9. Improves product shelf life.
10. Avoids dosing during night time.
11. Reduction in overall health cost.
12. Improves bioavailability of drugs.
13. Reduces the chances of drug accumulation in long term therapy.
14. Reduces the total drug usage [7-9]

Disadvantages of Modified Release:

1. Increased cost.
2. Dose dumping.
3. Increased potential for first pass clearance.
4. Need for additional patient education.
5. Unpredictable and often poor in vitro –in vivo correlations.
6. Reduced potential for dose adjustments.
7. Drug release period is influenced and limited by the GI residence time.
8. Delayed onset of action.
9. Once the drug release starts from these formulations then it is difficult to stop even if the patient or physician wants.
10. Toxicity due to dose dumping. [1,6,10,11]

The most effective formulation of modified-release is the one, which possess understanding of mechanism of drug release, particle size, shape, structure and molecular interactions. Based on the above criteria a new advanced manufacturing technology called as Accudep technology has been developed which is a highly-controlled electrostatic deposition process [12].
Delsys Pharmaceutical has been studying the application of dry powder deposition (Accudep) technology in the development of oral modified-release (controlled-release) products [12].
Delsys Pharmaceutical was formed in 1997 through collaborative investments by venture capital firms and the David Sarnoff Laboratory (Princeton, NJ), from which the company licensed its dry powder deposition technology [12].
Accudep technology is a new advanced technique, which is ideally suited for the manufacturing of pharmaceutical dosage forms. The technology is a highly-controlled electrostatic deposition process. It is a single continuous automated process, which is being applied to a range of product areas including intermediate-release dosage forms, super generic products and novel controlled-release formulations [13].
The main goal of this technique is to establish highly flexible delivery design that accommodate various drugs of diverse physicochemical characteristics and dose facilitate engineering of immediate as well as control-release of active ingredients [12].
The technology differs from the currently marketed controlled-release dosage forms in that: it excludes mixing, blending, granulation, drying, sizing and compression. Instead it utilizes the active ingredient in pure form and achieves controlled-release by the use of polymeric films of different release characteristics [12].
The principle involved in this technology is well known from classic physics i.e. opposite charges attract each other.
In 18th century coulomb measured the magnitude of electrostatic force and has introduced a formula:

$$F = Ke\frac{q1q2}{r2}$$

The most common example of electrostatic deposition is the xerography. The main steps in the process are attachment of film substrate to a patterned receiving module, controlled deposition of pure active powder onto the patterned regions on the substrate film, dose measurement, lamination to second film and processing into final dosage form [12].

Experimental

Accudep process:

1. In accudep technology, the pharmaceutical powder acting as toner is charged, and deposited to chamber where in dispersion and deposition takes place.

2. Deposition of material is accomplished by establishing a pattern of charges of one polarity on a substrate where deposition is desired, and delivering a supply of the material to be deposited in the form of small, oppositely charged particles.
3. The attractive coulomb's force created within the system speeds up and focuses the particles towards the desired regions of the substrate.
4. This interaction between charged particles and substrate provides an additional control mechanism for dosage size control.
5. Accurately addressing the variable factors with feedback controls sensors enables a quantitative model for designing and controlling automated systems for the deposition of materials by electrostatic deposition.
6. Accudep cores are prepared using accudep process to create controlled-release system.
7. The number of cores as well as the amount of drug per core can be varied to achieve a desirable sustained release profile.
8. In addition, two drugs can be co-delivered from the same delivery system. It is also feasible to control release rate by varying the number of polymeric film layers, their composition, and their thickness.
9. Furthermore, this delivery system is typically coated with an impermeable coating on the sides to constrain drug release.
10. This design provides yet another design variable: keeping either one or both ends open (i.e. without impermeable coating)
11. This design variable provides one to facilitate an immediate release component of the release profiles as well as providing an additional means for modulating the controlled-release portion of the drug.
12. The finished dosage form is intended to be elegant, easily swallowable, and economical to manufacture [12].

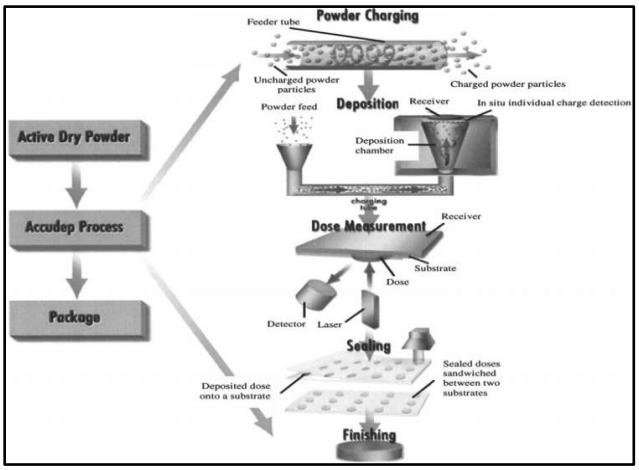

Figure 1. Accudep Process [12].

Description of Accudep Technology:

Application of Accudep Technology to Tablets:

A novel solid pharmaceutical dosage formulation of hydrophobic drugs is disclosed, which provides enhanced dissolution and improved bioavailability.

The formulation comprises:

1. A base substrate comprising a first polymer;
2. A deposit, comprising a therapeutic amount of a hydrophobic drug, deposited on the base substrate;
3. A cover substrate comprising a second polymer, the cover substrate covering the deposit and joined to the base substrate by a bond that encircles the deposit; and
4. A dissolution-enhancing amount of a surfactant, disposed within a carrier that is segregated from, but in contact with, the deposit.

In this, the hydrophobic drug is deposited electro statically on the base substrate.

Deposition of Drug:

In the above figure the "Deposition," of active ingredient ("drug") 14 is shown after being deposited on substrate 8, prior to sealing with cover layer 9. In the first drawing with the "Cover Film" ("Surfactant in Pouch"), the surfactant is incorporated on the cover layer ("cover film") 9 in a pouch 16, and cover layer 9 is aligned to place the pouch 16 in contact With active ingredient 14. The pouch material may be any polymer, and preferably the same material as substrate 8 or cover layer 9. Upon administration of the dosage form, during dissolution of cover layer 9 and/or substrate 8, pouch 16 similarly dissolves and releases the surfactant in the immediate vicinity of the drug, thereby improving drug dissolution.

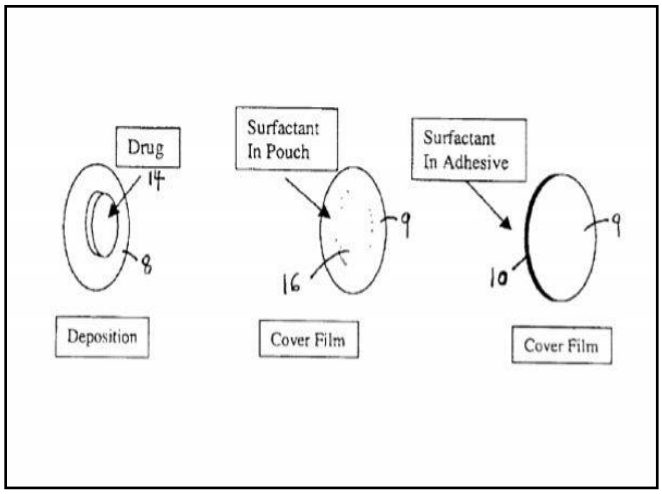

Figure 2. Components of various embodiments of unit forms [14]

A unique type of solid dosage form may be obtained by deposition of an active pharmaceutical ingredient on a pharmaceutically acceptable substrate. In the electrostatic deposition process, a cloud or stream of charged particles of the active ingredient is exposed to, or directed towards, a substrate, at the surface of which substrate a pattern of opposite charges has been established. In this fashion, a measured dosage of the active ingredient can be adhered to the substrate.

Although electrostatic drug deposition generally has certain benefits, including improved dose uniformity, certain problems still arise when the drug to be electro statically deposited is hydrophobic.

Specifically, the final dosage form may suffer from the same problems of poor dissolution and poor bioavailability that were discussed above with respect to conventional solid dosage forms of hydrophobic drugs. Moreover, the prior art approach, involving the intimate admixture of the hydrophobic drug and a surfactant, would be difficult or impossible to implement in the context of electrostatic deposition.

For example, if the drug and surfactant powders are to be blended prior to electrostatic deposition on the substrate, it may be difficult to obtain a suitably homogenous blend, or to maintain such homogeneity during the charging and delivery to the substrate. Moreover, co-deposition of the different powders would require that both powders behave similarly during the deposition, but this is difficult to achieve since different powders often have different optimum deposition parameters. In an extreme case, the surfactant may deposit only under a charge opposite that utilized for the active ingredient.

One possible solution would be to deposit the active ingredient and the surfactant sequentially. However, there may be difficulty in forming depositions on top of pre-existing depositions, due to charge dissipation [14].

Therefore, it would be desirable to provide a dosage form of a hydrophobic drug, wherein the problems of poor solubility and poor bioavailability, as well as the technical problems identified in the preceding paragraphs are overcome.

The hydrophobic drugs, and their pharmaceutically acceptable salts, which may be formulated are as follows:

1. **Analgesic and Anti-inflammatory Agents:** Acetaminophen, Ibuprofen, Salicylic acid.
2. **Anti-bacterial Agents:** Ciprofloxacin, Cefaclor, Penicillin.
3. **Anti-diabetic Agents:** Glipizide, Tolbutamide, Chlorpropamide.
4. **Anti-fungal Agents:** Fluconazole, Ketoconazole, Griseofulvin.
5. **Anti-thyroid Agents:** Carbimazole, Propyl thiouracil.
6. **Anti-Parkinsonian Agents:** Bromocriptine, Lysuride.
7. **Anti-neoplastic Agents:** Chlorambucil, Mercaptopurine, Procarbazine.
8. **Anti-malarial Agents:** Proguanil, Quinine, Chlorproguanil.
9. **Thyroid Agents:** Levothyroxine.
10. **Gastro intestinal Agents:** Omeprazole, Odansetron, Ranitidine [14].

Polymers:

Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics.

1. Hydroxy propyl methyl cellulose
2. Hydroxy propyl cellulose
3. Polyethylene glycol
4. Polyvinyl alcohol
5. Polyvinyl pyrrolidinone
6. Polysaccharide polymers
7. Acrylate polymers
8. Methacrylate polymers
9. Polyvinyl acetate
10. Methyl cellulose
11. Carboxy methylcellulose
12. Hydroxy ethyl cellulose
13. Ethyl cellulose
14. Polyethylene oxide
15. Polypropylene
16. Polyester and polyamide films,
17. Eudragits (that is, polymers and copolymers containing meth acrylic acid),
18. Starch-based polymers, gelatin [14].

Surfactants:

"Surfactant" acts as a surface active agent which displays wetting, detergent or soap-like qualities. The surfactants may be classified by an "HLB number." The HLB number provides a means for ranking surfactants based on the balance between the hydrophilic and lipophilic portions of the surfactant i.e., the higher the HLB number, the more hydrophilic the surfactant. Thus, the term "surfactant," as used herein, represents ionic and nonionic surfactants or Wetting agents commonly used in the formulation of pharmaceuticals, such as,

1. Benzalkonium chloride
2. Sorbitan fatty acid esters
3. Cetrimide
4. Sodium lauryl sulphate
5. Acetylate monoglycerides [14].

Application of Accudep Technology to Capsules:

1. Oral dose units called as accudep cores are prepared currently by using Accudep technology. The controlled-release systems under development consist of Accudep cores separated by erosional polymer film.

2. Figure 3 illustrates the example of six- layers, each of which contains three components. In each layer, an Accudep core is contained by a polymer ring.
3. The layers are separated by rate-controlling polymer film.
4. The dosage form is applied with an impermeable coating.
5. In this example, the top of the capsule is not coated, and is therefore available for drug release. If the layers dissolve sequentially pulsatile release will be achieved [12].

Variables Affecting Release Rates:

The following variables affect release rates in these systems are as follows:

1. One benefit of this approach is that the design variables are independent of one another and components can be tested separated, which simplifies formulation.
2. Another benefit is that the rate -controlling elements that dominate the release kinetics are isolated from the drug.
3. This further simplifies formulation, and minimizes exposure of the drug to excipients [12].

Dose Measurement Alternative:

The major advantage of this process is the ability to perform 100% dose inspection [13].

Research and Development:

1. Identification of suitable polymer films is the fore most step in the preparation of controlled –release dosage forms.
2. Polymeric films were screened using diffusion cells for potential suitability in the controlled-release dosage forms.
3. Acetaminophen was used as a marker compound to identify acceptable polymeric film during screening, and the media was pH 6.8 USP buffer solutions.
4. Figure 6 shows the screening results for two rate-controlling film candidates. Film A (cellulose based) was relatively impermeable for approximately 1 hour after exposure to the media, after which time, release was rapid and complete within another 2 hours.
5. In contrast, Film B (polyethylene oxide) released drug at a relatively constant rate for 16 hours.
6. Film A was found to be most suitable for a pulsatile release system when used in series.
7. Several batches of the controlled-release dosage form were prepared and evaluated by dissolution studies were performed in a USP II apparatus with pH 6.8 phosphate buffer at 37.4 ℃ and 50 RMP , using high performance liquid chromatography analysis.
8. Further development work was performed using Delsys Client Compound Number 30204 (CCN 30204), which is used as an adjunctive for chemotherapy [12].

Demonstration of Pulsatile Release:

1. As stated previously, it is possible to prepare controlled – release dosage forms to provide pulsatile dissolution profiles.
2. Figure 7 shows the dissolution data of a three layer system.
3. It is observed that one third of the total dose is released at approximately 3 hours intervals.
4. Composition of the film can easily control the number and duration of each pulse and also the number of drug containing layers used [12].

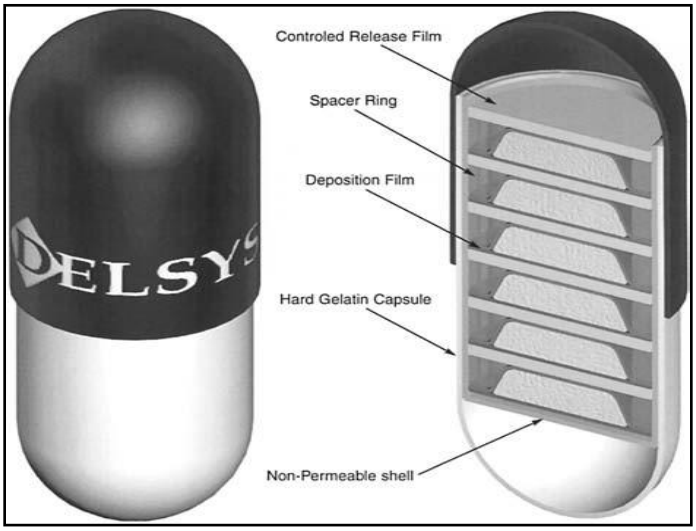

Figure 3. A Six layer dosage form housed in a gelatin capsule [12].

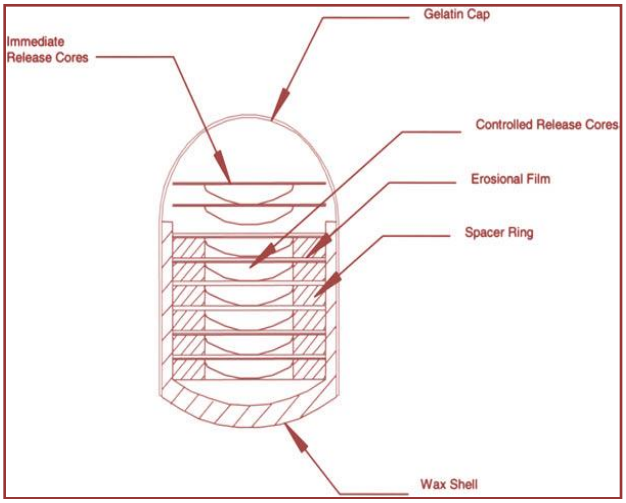

Figure 4. Configuration of an eight layer dosage form. In this example, the top two layers contain immediate-release cores while the remaining six layers are sandwiched between erosional controlled-release films [12].

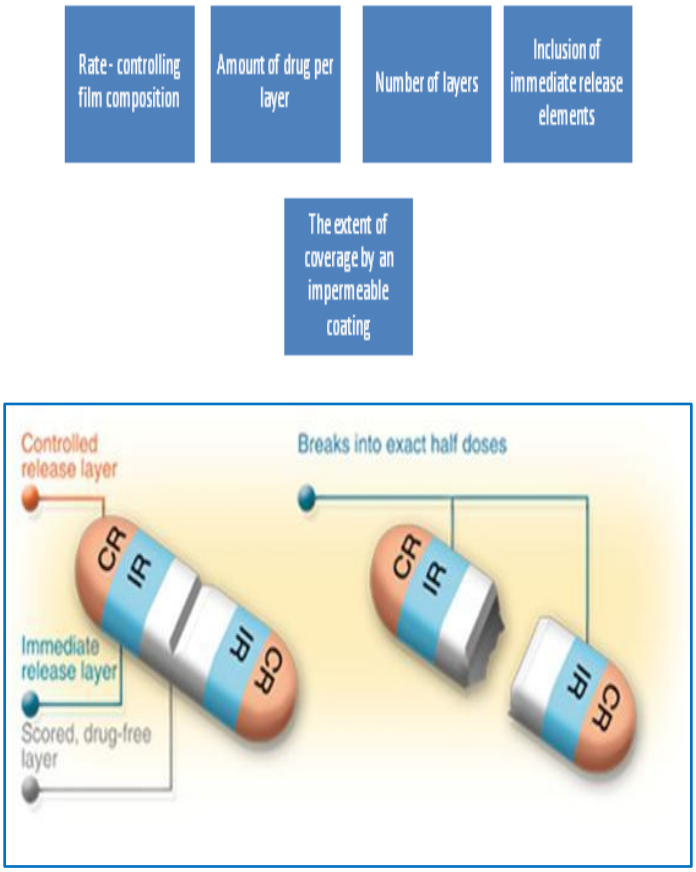

Figure 5. variables effecting release rates [13]

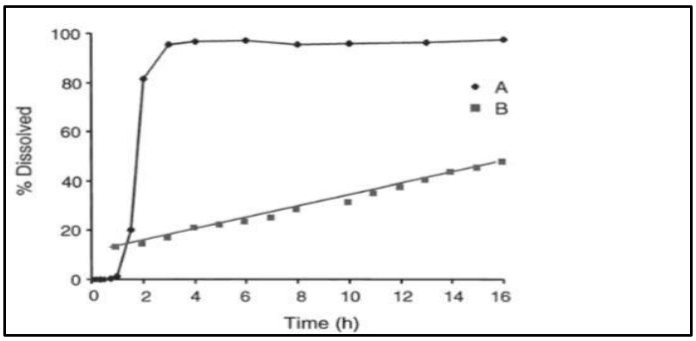

Figure 6. Transport of Acetaminophen Solution (pH 6.8) across two different films. Film A is 180 micro meter thick cellulose based film while Film B is composed of polyethylene oxide at the same thickness [12].

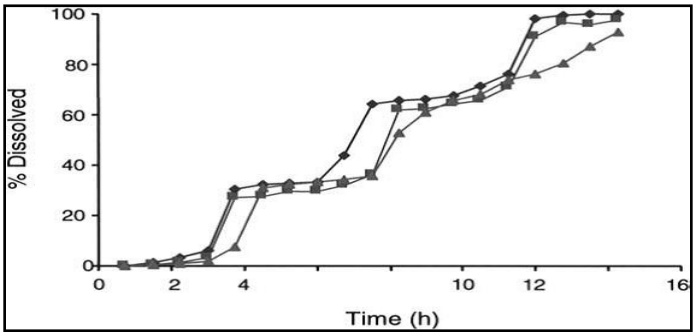

Figure 7. Dissolution of CCN 30204 from a three-layer dosage form at pH 6.1. The dosage form contains 8 mg of active drug in each layer. Each curve represents a single dosage form [12].

Effect of Rate-Controlling Film Composition:

1. In Figure 8, dissolution was performed on dosage forms prepared with the same rate-controlling films tested in the screening studies (see Figure 6).
2. Thus in one case, the rate-controlling film was prepared from the cellulosic material while the other formulation was prepared with polyethylene oxide film.
3. The correlation of data indicates that component screening can be used to select films for faster rates of dissolution or slower rates of dissolution [12].

Effect of Extent of Coverage by the Impermeable Coating:

1. Another model drug (theophylline) was used to study the effect of varying the surface area of the dosage form available for dissolution.
2. To compare surface area effects, one device was prepared as described previously where in release can occur only through one opening in the device.
3. In a second case, the available area for dissolution was double by developing a formulation of the same size, but with both the top and bottom surfaces uncoated (and therefore available for dissolution).
4. Figure 9 indicates a comparison of the two five-layer systems where in increasing the area available for dissolution increases the dissolution rate [12].

Animal Study:

1. An in vivo study was conducted with CCN 30204 using pig as an animal model.
2. The objective of this study was to evaluate the absorption profile of CCN 30204 from the Tackson CR dosage form (which utilizes the Accudep technology) compared with an immediate -release formulation (solution) of the drug.
3. The controlled-release dosage form was designed to provide an apparent constant absorption of the drug such that the plasma concentration over time would be relatively constant.
4. The solution (24 mg, Q 8h-3) was administered intra-duodenally.
5. The controlled-release dosage form (a six layer formulation containing a total of 24 mg) was also administered intra-duodenally.
6. Six pigs were each surgically prepared with two vascular catheters and a duodenal cannula.
7. One catheter was implanted into the right jugular vein, the second into the left internal jugular vein.

8. Both formulations (solution and controlled - release) were administered via cannula directly into the duodenum.
9. Pigs were fed at libitum until being starved overnight (16-20 h) prior to surgery
10. On the dosing day, the morning feed was withheld from the pigs and they received three – quarters of the total daily ration approximately 4 h after dosing with the controlled – release system or 4 h after the first dose of the solution.
11. Plasma samples were analyzed by LC/MS-MS.
12. The dosage forms were recovered upon elimination from the animal to provide transit time estimates as well as estimates of the extent of drug release.
13. A stability study was conducted with this batch of dosage forms.
14. The mean plasma levels following intra-duodenal administration of the solution and the controlled-release system are shown in figure 10.
15. While the relative bioavailability of CCN 30204 from the controlled -release dosage form was less than that from the immediate -release solution, these data generally support the fact that drug was released over an extended period of time, and as a result, absorption was prolonged and subsequent blood levels were elevated over a 24-h period.
16. This controlled-release system didn't show "dose dumping" but did provide significant release extension.
17. Also, 90% of the dose was released.
18. No degradation or change in dissolution of the product was observed after 3- months storage at 40°C, 75% RH [12].

Regulatory Issues:

1. The controlled-release delivery system under development should not encounter any significant regulatory hurdles.
2. The dosage form is composed entirely of compendia excipients, all of which are approved for oral consumption.
3. The size of the dosage form is within the acceptable range [12].

Advantages and Disadvantages of Accudep Technology:

Advantages:

1. Accudep technology provides lower manufacturing cost
2. More precise dosing
3. A cleaner / safer manufacturing environment
4. Fewer waste materials
5. Reduce labour and space requirements
6. Shortens process time
7. Some of the principles that can be exploited in the design of dosage form using the Accudep technology are :
   i. Diffusion barriers
   ii. Drug binding
   iii. Slow dissolution ands
   iv. Osmotically modified release.

Disadvantages:

1. Not all drugs can be blended with a given polymeric matrix.
2. Systems may be difficult to design.
3. Rupture can result in dose dumping.
4. Drug inactivation by contact with the polymeric matrix can be avoided.

Results and Discussion

In Accudep process, the pharmaceutical powder is charged, following powder charging, the drug powder is deposited onto a suitable polymer film. The resulting pattern of drug deposits is sealed and punched out to obtain discrete dose units. The units can be processed in a variety of ways including the creation of novel controlled-release dosage form. The design variable permits one to engineer an immediate release component of the release profiles as well as providing an additional means for modulating the controlled – release portion of the drug. The finished dosage form is intended to be elegant, easily swallow able, and economical to manufacture.

Accudep technology provides several benefits to the pharmaceutical industry including lower manufacturing cost, more precise dosing, a cleaner and safer manufacturing environment and fewer waste materials. The technology is configured as a fully-enclosed modular system which enhances environmental control, industrial hygiene, allowing for easy changes of product and capacity; it also includes automated quality control functions capable of evaluating the uniformity of doses. All of these benefits are accomplished with smaller capital investments, less space and a fewer people than current manufacturing process.

Current Market Utilization

Levothyroxine

1. Levothyroxine (LT4) is a low dose, potent drug with known content uniformity and stability problems.
2. Delsys is applying its proprietary Accudep electrostatic deposition technology to overcome the problems of content uniformity usually observed with low-dose, potent products.
3. Purpose: The objective of this investigation was to develop an immediate release dosage form for LT4 using Accudep technology.

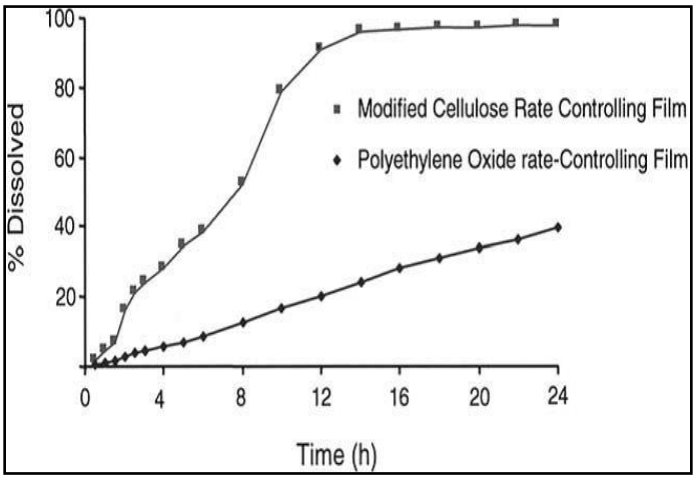

Figure 8. Dissolution of CCN 30204 from a six-layer dosage form at pH 6.8. Both formulations contain 4mg of active drug per layer for a total of 24 mg per dosage form. Each curve represents the average of 3 samples [12].

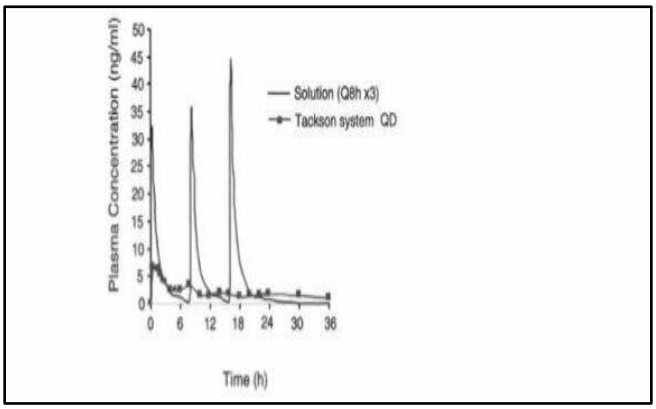

Figure 10. Blood levels of CCN 30204 in pigs. The six-layer dosage form is compared with a three times a day administration of an oral solution. The dosage forms contains 4 mg of CCNN 30204 per layer, for a total of 24 mg [12].

Odansetron

1. The drug substance, ondansetron, used in the study is an organic molecule. The drug is weak electrolyte and has a pKa of 7.5
2. Delsys is applying its proprietary Accudep electrostatic deposition technology to overcome the problems of content uniformity. Hard gelatin capsules were hand-filled with ondansetron to measure the effect of pH and particle size distribution on in vitro dissolution rates.
3. Drug recovered from the capsules at the end of human bioavailability study was consistent with the relative bioavailability from the controlled-release capsule formulations compared with the reference oral solution. Means to increase the solubility of ondansetron is currently under investigation

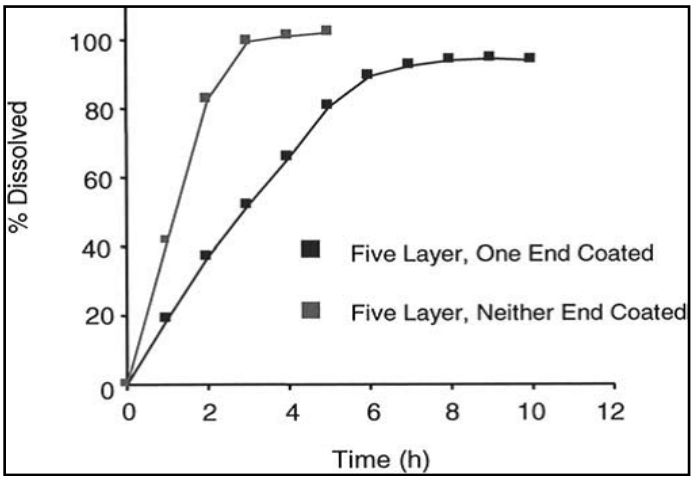

Figure 9. Dissolution of Theophylline from a five-layer dosage form. These layers each contain 5 mg of active drug. Each curve represents the average of three separate dosage forms [12].

Conclusion

Accudep technology can be used for preparing low dose, potent drug with known content uniformity and stable modified release dosage forms. It provides several benefits to the pharmaceutical industry including lower manufacture costs, more precise dosing, lower material, labour and space requirements and a shorter in-process time-line. The system also involves fewer steps and minimizes operator intervention in processing leading to essentially a one-step process.

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