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Active Film Coating

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ABSTRACT: An active coating on tablets is relatively new approach of drug delivery. Many potent molecules have issue of stability with traditional methods of tablet formulation. Hence, active film coating approach would be used to stabilize those molecules. The drug was sprayed onto active or non active tablet cores with coating material using conventional perforated film coating equipment. It enhances the drug product quality and stability. Also, this technique is industry feasible but its challenging operation with respect to desired amount of drug content and content uniformity. Hence, after understanding the degradation behavior of a drug product this technique is useful to design a stable formulation.

KEYWORDS: Active film coating, Drug substance degradation, Stable formulation, Active coated Tablets.

I. INTRODUCTION

Traditionally, Tablets are manufactured by mixing of active pharmaceutical ingredient (API) with excipients, granulation, compression and coating. Tablets are coated for a variety of reasons such as to enhance the appearance, identification, taste, protection (from light, oxygen, moisture), chemical stability or to create a modified release profile of the drug product.[1] In active film coating approach as the name indicates API is incorporated in film coating. API is incorporated with coating material to form active coating dispersion and this is sprayed on core tablets which are either active or non active. This process is known as "active film coating". Mostly conventional method of film coating is used for active film coating i.e. perforated pan coating.[2]

Advantages

1. Many potent molecules were found to be unstable in traditional unit process such as compression, wet granulation, dry granulation. To avoid these processes for compression sensitive, unstable molecules active film coating approach is useful.[2]
2. To avoid formation of impurity which are prone to degrade upon mixing with commonly used excipients.[2]
3. To achieve modify release profile of the drug substance. [3,4,5]
4. To formulate FDCs of incompatible active pharmaceutical ingredients (APIs). [3,4,5]
5. Industry feasible and economic approach as conventional methods were used for active film coating.

Limitation

This technique is applicable for formulation of low dose drugs only.

Formulation of Active film coated tablets

Pharmaceutical compositions are subject to stringent scrutiny of pharmaceutical authorities and industry on matters such as residual organic solvents, stability, content uniformity, economic and environment friendly manufacture. So, incorporating active pharmaceutical ingredient in a film coating and separating it from the compounds in a core with respect to requirements of authorities is a difficult task. Factors to be considered while formulation of Active film coated tablets are physical properties of API, desired release profile (immediate or modified), desired characteristics such as hardness, disintegration etc. The excipients used in formulation of Active film coated tablets are same as those which were used in formulation of conventional tablets.Steps involved in Formulation of Active film coated tablets are as follows: [2]

1. Formulation of tablet core (which is either active or non-active)

Conventional methods were used for compression to form tablet core. Excipients and/ or API were co-sifted then depending on the

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drugs/excipients characteristics direct compression, wet granulation or dry granulation method is selected. granules were dried until desired LOD achieved. dried granules were lubricated for sufficient time. Lubricated granules were compressed on suitable punches.

FDC tablets can be formulated with objective to keep two actives apart to minimize chemical interactions. In this case, one active could be included in the core tablet followed by another in coating (active film coating).

2. First layer coating or inner seal coating

Composition of coating material

Polymer/ film former: Depending on the desired release profile and compatibility of the API with them polymers are selected. for example- HPMC, PVA, EC, HPC, PEG, MHEC, etc.

Solvent: Solvents are selected based on solubility and compatibility of the API and polymer. for example- water, IPA etc.

Plasticizers, glidant and colorants are also selected depending upon compatibility of the API.

Preparation of coating dispersion

Coating materials were dissolved in a solvent under stirring and mixed well to form coating dispersion. /Core tablets were loaded on coating pan and preheated and then coated with coating dispersion in perforated film coating equipment until the desired weight was achieved.

3. Second layer coating or Active film coating

Preparation of drug solution or suspension: Coating material is same as it was used in first seal coating layer, additionally drug was added to coating dispersion. Drug to coating material concentration was investigated. Then drug and coating material were dissolved in a solvent under stirring and mixed well to form active coating dispersion.

Active coating

Seal coated tablets were loaded on coating pan and preheated and then coated with drug dispersion or suspension in perforated film coating equipment until the desired weight was achieved. Active coating was monitored throughout the process. Challenges were discussed further.

4.Third or outer protective coating layer (optional)

This is similar in composition with first coating layer. Preparation of coating material: coating material were dissolved in a solvent under stirring and mixed well to form coating dispersion. active coated tablets were loaded on coating pan and preheated and then coated with coating dispersion in perforated film coating equipment until the desired weight was achieved. This is protective layer to active coat Hence referred as Protective coating layer. But it is optional depending on the drug degradation pathways and stability.

Additionally, for formulating FDC of both sensitive molecules, both actives can be coated on the inert cores by applying in one coating layer or in two separate coating layers alternatively which were separated by an inert coating layer. FDC tablet formulation of such a molecule is even more challenging. One possible solution is to formulate a traditional tablet formulation for a molecule which is not sensitive to common pharmaceutical operations as the core tablets followed by depositing the sensitive molecule on the core tablets by active coating.

Challenges for formulation of active film coating

As the API is sprayed on the tablet cores in the active film coating. Hence, application of coating should be precise enough to ensure active ingredient as per labeled amount of dose. Therefore, monitoring of coating unit process is important.

In process monitoring of coating aimed at-

1. **Determining process endpoint**

The coating end point is determined by the amount of suspension sprayed or the weight gain of the core tablets. During the active coating, tablet samples are taken periodically and analysed not only for weight gain but also for the amount of API deposited by performing an in-process assay. [6] Due to variability in weight of core tablets and residual solvent content in coating layer results will be biased. so continuous and robust measurement technique would be useful such as NIR, Raman spectroscopy. [8,9,10]

2. **Measuring coating thickness**

Optical microscopy is used for measurement of thickness. Deformation in sample preparation process limits the use of this method. So, Non destructive terahertz pulsed imaging(TPI)

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technique is useful for quantification of coating thickness. [9,10]

3. **Analyzing coating variability/ uniformity/ Content uniformity**

Active film coated finished product should meet the requirements of uniformity of dosage units according to pharmacopoeia (USP<905>, Ph.Eur.2.9.40). To control on the spraying operation is vital for the content uniformity of the finished products.

Coating variability was systemically decreased by optimising coating composition, coating thickness, and other parameters of coating process in QbD based study. Hence, coating process should be optimized.[11]

Particle tracking methods such as Photographic and manual counting, Photometry, Magnetic resonance imaging (MRI), Nuclear magnetic resonance (NMR), Positron emission particle tracking (PEPT), Scanning electron microscopy (SEM), Image analysis, Particle tracking Velocimetry (PTV), Video imaging using charged coupled device (CCD) provides information on direction and orientation of tablet move through spray region. [12,13,14] Modelling techniques such as CFD, Discrete element modeling (DEM), Monte Carlo (MC) Simulations and Phenomenological and Population balance Models (PBM) will allow researchers to gain deeper understanding of coating process and streamline time release testing (RTRt) [14] Quality is monitored in line, at line, online and offline by process analytical technologies. Also, Guidance for Industry PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance was implentated.

Applications of active film coating

To enhance chemical stability

Saxagliptin is prone to undergo intramolecular cyclization reaction to form cyclic amidine which is not therapeutically active and therefore its formation is not desirable. This cyclization reaction occurs both in solid state and solution state. The rate of intramolecular cyclization of saxagliptin is accelerated when formulations are subject to wet granulation, roller compaction and tabletting and with commonly used excipients. Also, it increases when drug to excipient ratio increases. Because of these properties of saxagliptin formulation of conventional and stable dosage form is challenging. U.S. Pat. No. US2011/ 7951400B2, US2014/0072628 A1, 7,951,400 and US 2015/0250734 A1 discloses Pharmaceutically stable formultion of saxagliptin tablets with inner seal coating layer coated on the tablet core optionally comprising one or more polymers. A second coating layer comprising saxagliptin and one or more polymers and optionally, an outer potective coating layer comprising one or more polymers, wherein said core does not contain saxagliptin, or salts, hydrates thereof. The stable pharmaceutical composition does not exceed 0.15% of the cyclic amidine impurity at 40°C/75% relative humidity for 3 months.[2,15,16,17]

Peliglitazar, a PPAR α/γ agonist, was found to undergo acid as well as base catalyzed degradation. The acid catalyzed degradation led to the formation of benzylic alcohol and glycine carbamate and the base catalyzed degradation led to formation of p-hydroxyanisole and an amine degradant. In capsule formulations, the capsules with the lowest drug-loading exhibited maximum instability even at 25°C/60% RH storage condition. Incorporation of pH-modifiers to maintain 'micro-environmental pH' acidic did not prevent the formation of the base-catalyzed degradants. Traditional dry granulated tablet formulation which is qualitatively similar to the capsule formulations showed the presence of acid-catalyzed degradants even without the presence of an acidifying agent. On the other hand, traditional wet granulated tablet formulation showed mainly base-catalyzed degradants. Stability problems of the tablet formulation were aggravated because the potent molecule required low tablet strengths which resulted in low drug to excipient ratio. To stabilize the molecule, an active film-coating approach was explored. [18]

WO 2007/144175 discloses a pharmaceutical composition comprising a core with a first API and at least one coating comprising a second API. It is evident from the specification that ethanol solutions of API were used for film coating. It further discloses cellulose derivatives, acrylic polymers, polyvinyl pyrrolidone and polyethylene glycol as possible polymers to be used for film coating.

To achieve desired release profile

Loratadine is coated on extended release pseudoephedrine cores in Claritin-D™

Lovastatin was coated on extended release niacin core tablets in Advicor™

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US 6,656,503 B 1 is about producing a pharmaceutical tablet comprising a core and a film coating, wherein the core comprises an nonsteroidal anti-inflammatory drug (NSAID) and the film coating comprises a polymer and misoprostol.

Saxagliptin coated on Metformin extended release core tablets in KOMBIGLYZE XR US20l0/0074950 discloses anti-diabetic combination formulations containing a slow release biguanide, such as Metformin, and a DPP4 inhibitor, such as Saxagliptin. The formulations contain a tablet core containing the biguanide in a slow release form. The cores are then provided with a sub coat layer and a seal coating layer, upon which a layer containing the DPP4 inhibitor is applied. [19]

EP 2259676 A1 discloses Anti-diabetic combination formulations containing combination of Metformin and a DPP4 inhibitor, such as Sitagliptin. The formulations contain a tablet core containing the biguanide. The cores are then provided With a sub coat layer and a seal coating layer, upon Which a layer containing the DPP4 inhibitor is Sitagliptin applied. [20]

Fixed-dose combination tablets (FCTs) by coating a Glimepiride immediate-release (IR) layer on a Metformin hydrochloride extended-release (ER) core tablet.

Table 1: Marketed Formulations

Drug/ Dose	Tradename	Company
Saxagliptin Tablets 2.5mg, 5mg	ONGLYZA®	Bristol-Mayers Squibb
Saxagliptin and Metformin Tablets 2.5mg/1000mg, 5mg/1000mg, 5mg/500mg	KOMBIGLYZE XR	Bristol-Mayers Squibb
Loratadine and Pseudoephedrine Tablets	Claritin-D®	Schering -Plough corporation
Lovastatin and Niacin Tablets	Advicor™	Physicians Total Care, Inc.

II. CONCLUSION

Recent developments in traditional technology has made stable formulations of critical molecules with easy unit processes for formulators. Hence, active film coating approach can be use to stabilize those molecules. The drug was sprayed onto active or non active tablet cores with coating material using conventional coating methods. In this way, An active coating on tablets is newer approach of drug delivery. Active film coating is easy, industry feasible and robust technique. It is useful in development of FDCs and controlled release formulations of sensitive molecules. Some challenges such as desired amount of drug content and content uniformity need to focus during formulation. Hence, after understanding the degradation behavior of a drug product this technique is useful to design a stable formulation.

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