



A REVIEW OF PRODUCT STABILITY AND QUALITY CONSIDERATIONS OF FORMULATION STRATEGIES AND SOLVENT FREE MANUFACTURING TECHNOLOGIES FOR ESTRADIOL

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1. INTRODUCTION

Estradiol (E_2) is a form of estrogen that regulates multiple functions in human body (Brann et al., 2007). It controls ovulation and the development of female sex characteristics, being classically considered a reproductive hormone, due to its well-known role in feedback signaling in the hypothalamic-pituitary-ovarian axis.^[1,2]

Estrogens refer to any substance, natural or synthetic, that mimics the effects of the natural hormone. The three majors naturally occurring forms of estrogens are estrone, E_2 , and estriol, being E_2 the most potent and prevalent form, although several metabolites also have estrogenic hormonal activity. The actions of estrogens are mediated by estrogen receptors (ER). ER α was first described in the 1960s. These homologous receptors, described as ligand-activated nuclear transcription factors are predominately present in nucleus and cytoplasm, with less than 2% on cellular membrane. Each ER exhibits differential tissue expression patterns, but both regulate gene transcription through classical genomic pathways, or by modulating cellular signaling pathways such as the mitogen-activated protein kinases (MAPKs)/extracellular signal-regulated kinases (ERKs) modulation of intracellular calcium, cyclic adenosine monophosphate (cAMP) production and regulation of phosphatidylinositol 3-kinase (PI3Ks).^[3,4,5]

In the late 1990s, the G protein-coupled estrogen receptor 1 (GPER or GPR30) was identified as a novel estrogen receptor. It was described as an orphan receptor belonging to the family of 7-transmembrane spanning G protein-coupled receptors. In 2000, Filardo et al. demonstrated that E_2 -mediated activation of ERK1/2 was dependent on the expression of this receptor, and named it GPR30 (Filardo et al., 2000).^[6,7]

Estrogens mediate genomic effects through the classical ERs that are characterized by changes in gene transcription and occur in the time frame of hours to days. Furthermore, it was also reported that estrogens mediate a variety of “rapid” cellular responses that occur in the time frame of seconds to minutes, inconsistent with *de novo* transcription and protein synthesis. These rapid estrogen-mediated effects have been associated with the activation of membrane-associated ERs and are referred as “non-genomic”. The signaling pathways that triggers these rapid estrogen-mediated effects are diverse and can be induced by ER β present near or at the plasma membrane by the translocation of ER β to the plasma membrane after E_2 treatment, by the interaction of non-membrane ER α and ER β with integral membrane proteins or through the activation of GPER. In addition to the rapid GPER-mediated effects triggered by E_2 it was also described that GPER selective activation has also the ability to alter gene expression (Kanda and Watanabe, 2004). E_2 , as well as many other compounds that bind to classical ERs have also been demonstrated to bind to or activate GPER. The discovery of GPER-selective ligands aided the research into the specific activities of GPER., using a combination of virtual and biomolecular screening, identified the first selective GPER agonist, a non-steroidal compound named G1.^[8,9,10]

The modulation of GPER was complemented with the identification of two selective antagonists, named G15 and G36. Binding studies about the affinity of these three selective ligands of GPER demonstrated that G1 has a binding affinity of about 11 nM compared to 3–6 nM for estrogen. Whereas G15 and G36 presents a similar affinity of approximately 20 nM but with G36 showing a decreased binding and activation of ERα compared to G15.^[11,12]

Other compounds were described as having significant affinity to GPER, but in a non-selective manner, include 4-hydroxytamoxifen (the active metabolite of Tamoxifen) Since the identification of the GPER-selective ligands an increasing number of studies addressing the potential cellular and physiological effects of GPER selective activation in numerous systems including the central nervous system (CNS) were published.^[13,14]

The emerging notion that E₂ can act in multiple areas of the brain led to an increased focus on its effects on neuronal physiology and neuroplasticity. *In vitro* and *in vivo* studies indicated that E₂ is a potent physiological modulator of the CNS and participates in processes such as neurogenesis, regulation of neurotrophic factors expression and regulation of antioxidant mechanisms. Estrogens were also associated with the regulation of cognitive Processing.^[15,16]

Selective activation of GPER by its agonist G1 enhances cognitive processes, such as learning and memory, in a manner similar to E₂. Besides, GPER is highly enriched in the brain and greatly expressed at the synapses, being involved in the rapid regulation of hippocampal dendritic morphology and synaptic plasticity. G1 enhances recognition memory tasks and social recognition. In agreement with this, chronic treatment with the GPER selective antagonist G15 impairs acquisition of a spatial learning task.

Over the recent years this receptor emerged has a potential therapeutic target to induce neuroprotection. This hypothesis was based on the ability of its selective agents to mimic the effects of E₂ without the feminizing or other adverse effects (Prossnitz and Barton, 2012). Activation of GPER may replicate the beneficial effects of E₂ in the brain avoiding the side effects associated with estrogen replacement therapies, like increased risk of coronary heart disease, breast cancer and stroke. In this review, we explore the expression pattern and signaling pathways of GPER, its role in the CNS, and relevance to neurological disorders.^[17,18,19]

IMPORTANT ROLE AND FUNCTIONS OF ESTRADIOL

Estradiol plays a central role in many physiological processes, particularly in the female reproductive system. Estradiol is essential for the regulation of the menstrual cycle. During the follicular phase of the menstrual cycle,

estradiol levels gradually rise, which stimulates the growth of the ovarian follicles. This prepares the uterus for potential pregnancy by thickening the endometrial lining. At ovulation, estradiol levels peak, triggering the release of the egg.^[20]

After ovulation, estradiol works with progesterone to support the early stages of pregnancy or regulate the next menstrual cycle. It is key to the process of ovulation, the release of an egg from the ovary. It helps in the maturation of the egg and promotes the release of Luteinizing Hormone (LH), which is responsible for triggering ovulation. It is involved in the development of secondary sexual characteristics, such as the growth of breasts. It also contributes to the development of the milk ducts in preparation for lactation, though prolactin is the primary hormone responsible for milk production.^[21,22]

Estradiol plays a significant role in maintaining bone density. It helps in the regulation of bone remodeling by balancing the activity of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells).^[23]

Low estradiol levels, especially during menopause, can lead to a decrease in bone mass, increasing the risk of osteoporosis. Estradiol has protective effects on cardiovascular health.

It helps maintain healthy cholesterol levels by increasing High-Density Lipoprotein (HDL) cholesterol, often referred to as "good cholesterol." Estradiol also promotes the dilation of blood vessels, improving blood flow and regulating blood pressure. Estradiol influences mood and emotional well-being.^[24]

Fluctuating levels of estradiol, especially during the menstrual cycle, pregnancy, or menopause, can affect mood, leading to symptoms like irritability, anxiety, or depression.

While estradiol is often associated with female health, it also plays an important role in men's health. In men, estradiol is produced in smaller amounts, but it is still essential for several physiological processes.

In men, estradiol is involved in the regulation of spermatogenesis (the production of sperm). It works with testosterone to maintain the health and function of the male reproductive system. Just as in women, estradiol is important for maintaining bone density in men.

Lower levels of estradiol in men can contribute to a decrease in bone mass and an increased risk of fractures, particularly in older age.^[25]

Estradiol has a role in brain function and cognitive health in men as well. It has been shown to have neuroprotective effects, influencing memory and learning.

2. FORMULATION STRATEGIES AND SOLVENT FREE MANUFACTURING TECHNOLOGIES FOR ESTRADIOL PRODUCT STABILITY AND QUALITY CONSIDERATIONS

1. Stability of Extruded 17 β -Estradiol Solid Dispersions

Recrystallization is one of the main problems concerning the stability of solid dispersions. Different analytical methods were applied showing that no recrystallization occurred after treating melt extruded solid dispersions with 17 β -Estradiol as the model drug with heat or water vapor. A skillful choice of excipients—a combination of polymers and additives—could be the reason for improving the stability. The requirements of the USP 23 for Estradiol tablets of 75% dissolved drug after 60 min were fulfilled after storing the tablets for 6 months at 40°C/75% RH. By observing the change in glass transition temperature, DSC analysis showed that the solid dispersions were stable against thermal stress. Isothermal microcalorimetry as well as moisture absorption gravimetry were methods to prove the stability of the solid dispersions against water vapor.^[26]

2. Roller Compaction and Dry granulation

Roll compaction/dry granulation (RCDG) is an agglomeration process of growing importance. New machine generations and improvements in instrumentation and process control have resulted in an increasing number of pharmaceutical applications of RCDG. This literature review illustrates the progress and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.^[27]

3. Comprehensive review on modern techniques of granulation in pharmaceutical solid dosage forms.

This comprehensive review explores modern granulation techniques in pharmaceutical dosage forms along with conventional methods, focusing on dry granulation and wet granulation. Dry granulation techniques, including slugging, roller compaction, and pneumatic dry granulation, are dissected with thorough analyses of their processing methods, advantages, disadvantages, and diverse applications. The article delves into eleven wet granulation techniques, offering insights into high-shear granulation, low-shear granulation, fluidized bed granulation, reverse wet granulation, steam granulation, moisture-activated dry granulation, melt granulation, freeze-dry granulation, foam granulation, thermal adhesion, and twin-screw wet granulation. Each method is scrutinized, providing a comprehensive understanding of its processing steps, merits, drawbacks, and practical applications in pharmaceutical manufacturing. The article serves as a valuable resource for researchers, pharmaceutical professionals, and students, offering a nuanced exploration of diverse granulation techniques vital in drug formulation. This synthesis of information aims to enhance the understanding of granulation

processes, facilitating informed decision-making in pharmaceutical development and manufacturing.^[28]

4. Pneumatic dry granulation: potential to improve roller compaction technology in drug manufacture.

Solid dosage form manufacture still remains the most common in the production of pharmaceutical products. Established granulation processes can benefit from novel technical improvements, which can in turn enhance the behavior and properties of the process intermediates, that is, granules. These improvements in the manufacturing process can ultimately shorten development times, provide processing solutions for challenging materials and improve quality of drug delivery systems.

The aim of this review is to give the reader an overview of the latest trends in research with regard to roller compaction technology. Pneumatic dry granulation is also discussed as a new development with the potential to improve and extend the use of dry granulation processes, which can result in a substantial contribution to drug delivery system development and drug product manufacture.

Dry granulation techniques, and more specifically roller compaction, can provide many advantages over the more established wet granulation techniques. There are still problems with roller compaction such as high amounts of fines and poor flow of granulate. Technical innovations that improve existing processes will have a considerable impact on development times and contribute to improved material processability and behavior of the end product. Pneumatic dry granulation has the potential to provide such alternatives.^[29]

5. Roll Compaction/Dry Granulation (Rcdg): Technologies and Their Applications In Drug Delivery and Development.

Recently molecular modelling, high throughput screening, combinatorial and parallel synthesis techniques have increased the number of drug molecules ready for formulation into suitable delivery systems. However, many of these drugs have poor physicochemical properties. Oral route is the most preferred route of drug administration due to its convenience, highest patient compliance and low production cost. However, formulating drugs having inconsistent low densities, with poor flow properties and compressibility in solid dosage forms poses a major challenge for the formulation scientist. Roll Compaction/Dry Granulation (RCDG) is a pressure agglomeration method in which powder(s) is densified by passing between two counter-rotating rolls. The RCDG technique has significant effect on fluidity, compressibility and compactibility of the pharmaceutical active pharmaceutical ingredients and excipients consequently, influencing drug release profile and tablet properties. There is an increasing interest of industry and academia in RCDG technique, since RCDG excludes any liquid solvent or binder solution and is environmentally

safe and cost-effective. Various mathematical models for analysis of powder compaction are reported that allow better understanding of process parameters, leading to its better design and control. However, losses of tabletability/reworkability, high fines fraction, non-homogeneity of compacts are few challenges in formulation development using roll compaction. These can be overcome by judicious optimization of process parameters and selection of appropriate excipients. This article aims at discussing the current technological advancements related to roll compactor devices available for dry granulation, their working principle, benefits and challenges of RCDG technology along with various applications relevant to the pharmaceutical field.^[30]

6. Influence of in line monitored fluid bed granulation process parameters on the stability of Ethinylestradiol

Ethinylestradiol (EE) as a highly active and low dosed compound is prone to oxidative degradation. The stability of the drug substance is therefore a critical parameter that has to be considered during drug formulation. Beside the stability of the drug substance, granule particle size and moisture are critical quality attributes (CQA) of the fluid bed granulation process which influence the tableting ability of the resulting granules. CQA should therefore be monitored during the production process by process analytic technology (PAT) according to ICH Q8. This work focusses on the effects of drying conditions on the stability of EE in a fluid-bed granulation process. We quantified EE degradation products 6- α -hydroxy-EE, 6- β -hydroxy-EE, 9(11)-dehydro-EE and 6-oxo-EE during long time storage and accelerated conditions. PAT-tools that monitor granule particle size (Spatial filtering technology) and granule moisture (Microwave resonance technology) were applied and compared with off-line methods. We found a relevant influence of residual granule moisture and thermic stress applied during granulation on the storage stability of EE, whereas no degradation was found immediately after processing. Hence, we conclude that drying parameters have a relevant influence on long term EE stability.^[31]

7. Recent studies on the processes and formulation impacts in the development of solid dispersions by hot-melt extrusion

Industrial-scale pharmaceutical applications still face many challenges in overcoming the low absorption and bioavailability of poorly water-soluble drugs. Hot-melt extrusion has emerged as a promising approach with continuous processing on an industrial scale for the preparation of drug delivery systems. Many reviews have mentioned the potential applications, processes, principles and advantages and disadvantages of hot-melt extrusion in the pharmaceutical industry. However, a focus on the recent progress of hot-melt extrusion, which investigates the impacts of processes and formulations of solid dispersions of poorly water-soluble drugs, is missing. In this review, various factors, including

polymers, drug properties, additives and surfactants, in solid dispersion SD formulations by hot-melt extrusion will be discussed. Moreover, the effects of the hot-melt extrusion process on the physicochemical properties of solid dispersions will be mentioned. The utilization of molecular interactions in hot-melt extrusion to improve drug stability will also be described. Overall, this summary of recent studies on solid dispersion by hot-melt extrusion will provide perspectives and effectiveness for the development of formulations containing poorly water-soluble drugs.^[32]

8. Strategies to improve the stability of amorphous solid dispersions in view of the hot melt extrusion (HME) method

Oral administration of drugs is preferred over other routes for several reasons: it is non-invasive, easy to administer, and easy to store. However, drug formulation for oral administration is often hindered by the drug's poor solubility, which limits its bioavailability and reduces its commercial value. As a solution, amorphous solid dispersion (ASD) was introduced as a drug formulation method that improves drug solubility by changing the molecular structure of the drugs from crystalline to amorphous. The hot melt extrusion (HME) method is emerging in the pharmaceutical industry as an alternative to manufacture ASD. However, despite solving solubility issues, ASD also exposes the drug to a high risk of crystallisation, either during processing or storage. Formulating a successful oral administration drug using ASD requires optimisation of the formulation, polymers, and HME manufacturing processes applied. This review presents some important considerations in ASD formulation, including strategies to improve the stability of the final product using HME to allow more new drugs to be formulated using this method.^[33]

9. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation

Hot-melt extrusion (HME) is a promising technology for the production of new chemical entities in the developmental pipeline and for improving products already on the market. In drug discovery and development, industry estimates that more than 50% of active pharmaceutical ingredients currently used belong to the biopharmaceutical classification system II (BCS class II), which are characterized as poorly water-soluble compounds and result in formulations with low bioavailability. Therefore, there is a critical need for the pharmaceutical industry to develop formulations that will enhance the solubility and ultimately the bioavailability of these compounds. HME technology also offers an opportunity to earn intellectual property, which is evident from an increasing number of patents and publications that have included it as a novel pharmaceutical formulation technology over the past decades. This review had a threefold objective. First, it sought to provide an overview of HME principles and present detailed engineered extrusion equipment designs. Second, it included a number of published reports on the

application of HME techniques that covered the fields of solid dispersions, microencapsulation, taste masking, targeted drug delivery systems, sustained release, films, nanotechnology, floating drug delivery systems, implants, and continuous manufacturing using the wet granulation process. Lastly, this review discussed the importance of using the quality by design approach in drug development, evaluated the process analytical technology used in pharmaceutical HME monitoring and control, discussed techniques used in HME, and emphasized the potential for monitoring and controlling hot-melt technology.^[34]

10. Co-Crystallization Approach to Enhance the Stability of Moisture-Sensitive Drugs

Stability is an essential quality attribute of any pharmaceutical formulation. Poor stability can change the color and physical appearance of a drug, directly impacting the patient's perception. Unstable drug products may also face loss of active pharmaceutical ingredients (APIs) and degradation, making the medicine ineffective and toxic. Moisture content is known to be the leading cause of the degradation of nearly 50% of medicinal products, leading to impurities in solid dose formulations. The polarity of the atoms in an API and the surface chemistry of API particles majorly influence the affinity towards water molecules. Moisture induces chemical reactions, including free water that has also been identified as an important factor in determining drug product stability. Among the various approaches, crystal engineering and specifically co-crystals, have a proven ability to increase the stability of moisture-sensitive APIs. Other approaches, such as changing the salt form, can lead to solubility issues, thus making the co-crystal approach more suited to enhancing hygroscopic stability. There are many reported studies where co-crystals have exhibited reduced hygroscopicity compared to pure API, thereby improving the product's stability. In this review, the authors focus on recent updates and trends in these studies related to improving the hygroscopic stability of compounds, discuss the reasons behind the enhanced stability, and briefly discuss the screening of co-formers for moisture-sensitive drugs.^[35]

11. Package selection for moisture protection for solid, oral drug products

This review describes how best to select the appropriate packaging options for solid, oral drug products based on both chemical and physical stability, with respect to moisture protection. This process combines an accounting for the initial moisture content of dosage form components, moisture transfer into (out of) packaging based on a moisture vapor transfer rate (MVTR), and equilibration between drug products and desiccants based on their moisture sorption isotherms to provide an estimate of the instantaneous relative humidity (RH) within the packaging. This time-based RH is calculationally combined with a moisture-sensitive Arrhenius equation (determined using the accelerated

stability assessment program, ASAP) to predict the drug product's chemical stability over time as a function of storage conditions and packaging options. While physical stability of dosage forms with respect to moisture has been less well documented, a process is recommended based on the threshold RH at which changes (e.g., dosage form dissolution, tablet hardness, drug form) become problematic. The overall process described allows packaging to be determined for a drug product scientifically, with the effect of any changes to storage conditions or packaging to be explicitly accounted for.^[36]

12. Quality-by-design in hot melt extrusion based amorphous solid dispersions: An industrial perspective on product development

An industrially feasible approach to overcome the solubility and bioavailability limitations of poorly soluble active pharmaceutical ingredients is the development of amorphous solid dispersions (ASDs) using hot-melt extrusion (HME) technique. The application of Quality by Design (QbD) had a profound impact on the development of HME-based ASDs. The formulation and process optimization of ASDs manufactured via HME techniques require an understanding of critical quality attributes, critical material attributes, critical process parameters, risk assessment tools, and experimental designs. The knowledge gained from each of these QbD elements helps ensure the consistency of product quality. The selection and implementation of appropriate Design of Experiments (DoE) methodology to screen and optimize the formulation and process variables remain a major challenge. This review provides a comprehensive overview on QbD concepts in HME-based ASDs with an emphasis on DoE methodologies. Further, the information provided in this review can assist researchers in selecting a suitable design with optimal experimental conditions. Specifically, this review has focused on the prediction of drug-polymer miscibility, the elements and sequence of QbD, and various screening and optimization designs, to provide insights into the formulation and process variables that are encountered routinely in the production of HME-based ASDs.^[37]

3. CONCLUSION

Estradiol is an important estrogen hormone, and the development of suitable pharmaceutical formulations requires careful consideration of formulation strategies, manufacturing processes, product stability, and quality attributes. This review highlights the potential of solvent-free manufacturing technologies, particularly roller compaction, dry granulation, and hot-melt extrusion, in pharmaceutical formulation development. These technologies can reduce or eliminate the need for liquid solvents during processing and may offer advantages in process efficiency, environmental sustainability, and product quality.

The stability of pharmaceutical formulations depends on several factors, including drug–excipient compatibility, polymer selection, processing temperature, moisture exposure, and storage conditions. Appropriate formulation strategies and careful optimisation of manufacturing parameters are therefore essential to maintain the physical and chemical stability of the final product. In addition, suitable packaging systems, moisture protection strategies, and stability testing play important roles in preserving product quality throughout its shelf life.

The application of Quality by Design (QbD) principles and Process Analytical Technology (PAT) can further support the identification and control of critical material attributes, critical process parameters, and critical quality attributes during pharmaceutical manufacturing. However, each solvent-free technology has its own limitations, and its suitability must be evaluated according to the physicochemical properties and thermal stability of the drug substance.

In conclusion, solvent-free manufacturing technologies offer promising approaches for developing pharmaceutical formulations with consistent quality and improved manufacturing efficiency. Further experimental studies are required to establish the most suitable solvent-free formulation strategy for estradiol, particularly regarding moisture-related stability, drug–excipient compatibility, degradation behaviour, and long-term storage performance. Such studies may contribute to the development of stable, reliable, and high-quality estradiol pharmaceutical products.

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