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Review Article

A Concise review on application of solid lipids and various techniques in the formulation development

Sandip Barku Ahire*, Ravindra Keshavrao Kamble

Department of Pharmaceutics, Faculty of Pharmacy, Bhupal Nobles' University, Old Station Road, Udaipur- 313001. Rajasthan, India

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*Address for Correspondence:

Department of Pharmaceutics, Faculty of Pharmacy, Bhupal Nobles' University, Old Station Road, Udaipur- 313001. Rajasthan, India

Abstract

Lipids have wide range of applications in food and pharmaceuticals. The pharmaceuticals application of lipid is to improve solubility of drug also helps to improve the bioavailability. The dissolution/dissolving phase, which is probably the rate-limiting component for oral absorption of poorly water-soluble drugs, is eliminated by pre-dissolving pharmaceuticals in lipids, surfactants, or combinations of lipid excipients and surfactants. The most widely used co-solvents, together with lipid excipients, are propylene glycol, glycerol, and polyethylene glycols-400, poloxamer etc. various technologies are used such as melt extrusion, melt granulation for preparation of lipid based oral modified released dosage forms. This review summaries the overview of the lipid excipients in terms of their classification, methods of absorption, and lipid-based product development. The manufacture of solid and semi-solid lipid formulations using various methodologies, applications, phase behaviour, and the regulatory outlook of lipid excipients are covered.

Keywords: Solid lipids, lipid classification, solidification techniques, modified released.

1. Introduction

Since its introduction to the market in 1981, oral lipid-based drugs have grown to comprise around 3% of all oral formulations sold commercially[1]. Drugs having poor bioavailability and solubility can be delivered using formulations based on lipids [2]. Also this lipid based formulations gives therapeutics advantages [3-6]. As lipids are metabolized and absorbed by the digestive system, many substances that are similar to lipids are absorbed by the lymphatic system instead of the liver and pass out of the body via the thoracic lymph duct[7]. Vegetable oils, Fatty acids, triglycerides, also their derivatives are examples of lipids that can exist in the form of numerous particles that are solid, semisolid, or liquid. Those lipids that have higher melting points it means above body temperature they will be easily converted to solid dosage form, where as those lipids that are liquid as well as semisolid that will be suitably converted to multiparticulate dosage forms by the adsorption process on compatible pharmaceutical additives[8]. Lipids are currently used extensively in the manufacturing of numerous formulations employing inventive adaptations and modifications of traditional machinery with a moderately simple method. Several methods are used, including spray cooling, adsorption on a solid support, pastillation, melt extrusion, melt granulation, and spheronization[9]. These methods improve the flow of bulk lipids by dissolving lipids into certain size solid particles (powder, granules, or pellets) and then placing them in capsules, bags, or even in dispersible tablets.

Lipids are employed in a variety of ways in pharmacological dosage forms (Table 1), including:

1) Increasing the processing efficiency or maintaining the drugs preferred physical condition

2) Modification of the drug's cellular or systemic absorption

3) Improved drug targeting

4) Extended or more controlled medication delivery.

Table 1: Benefits of lipid-based delivery systems[10, 11]

Benefits related to biopharmaceuticals	Benefits Related to Product Development
Lipid melts helps to increase the solubility as well as bioavailability of drugs.	Lipid materials can also be processed in a fixed dosage form by adsorbing them to the right additives.
The gastrointestinal tract's absorption and digestion of lipids promotes the uptake of entrapped drugs into the lymphatic system, bypassing the liver.	Produced utilizing traditional methods and tools, with processing options that are flexible and contemporary techniques that enable cost-effective manufacture.
Enhanced drug micellar solubilization induced by bile	Increasing formulation flexibility and knowledge of functional excipients
lipids that are digestible and used for taste masking and non-digestible used for release retardants action	Helps to prevent modification in the release kinetics of drugs that are influenced by adsorption

2. Classification of lipid excipients

2.1 Fatty Acids and their Related Derivatives

Long-chain fatty acids such as benzoic acid, stearic acid, and palmitic acid are used to deliver continuous release in oral medication. Because they react chemically with other solids and have the best processing properties, such as uniform distribution of particles, enhanced compression, and control the final release of active compounds, fatty acid salts such as aluminum, calcium, and magnesium are often used on tablets[12].

2.2 Wax, neutral lipids, and oils

Mono, di, as well triglycerides are produced through the esterification of fatty acids to glycerol. Chemically altered natural triglycerides contain substances that can be used to create medication delivery systems such as glyceryl distearate, mineral oil, stearoyl polyoxyl-6 glycerides, olive oil as well as ethyl ester, glycerol monostearate, and hydrogenated vegetable oils[13].

2.2.1 Phospholipids

In order to form phospholipids, glycerides must undergo a more complicated change of their terminal hydroxyl. The common phospholipid heads include glycerol and glycerol esters, as well as ethanolamine, serine, choline, inositol, and inositol phosphate. Amphipathic phospholipids are utilized as an oral capsule medication and combine easily with emulsifiers and dispersants[14].

2.2.2 Glycolipids

Glycolipids are compounds that develop as the sugar mixture attaches to the glyceride's backbone. Traditional glycol lipids, which include glycosyl glycerides as well as ceramides, are uncommon in pharmaceutical products due to their scarcity and expensive cost, however, glycosyl modifications may be employed to incorporate targeting mechanisms into lipid formulas[15].

3. Advantages of lipids use as drug carrier

Lipid-based formulas increase the bioavailability of drugs. Pharmacological half-life can be extended through lipidation therefore the use of lipid carriers, enhancing pharmacokinetics and enabling less frequent dosing. When lipids are present in the digestive tract, bile salts are encouraged to be released, simulating a partially fed state. Bile salts cause the drug to emulsify, improving its in vivo solubility as it is only moderately soluble in gastrointestinal fluid. The solubilized compounds' digestion is then accelerated, which inevitably raises oral bioavailability[16]. Due to their stability across a range of pH and moisture levels, lipids constitute an effective barrier for certain sensitive drugs towards gastrointestinal or environmental conditions. Lipids substances are non-cytotoxic and biodegradable, they have a long history of being safe for use[17]. Solid lipids have the additional advantage of maintaining their structural integrity, which enables them to resist the effects of enzymes in vivo for an adequate period of time[18]. Lipids offer an environment that is hydrophobic and resistant to enzymes, which help to delay the release of the drug that has been loaded and result in a regulated drug release[19].

4. Manufacturing benefits of lipids substances as drug carriers

Lipids have significant advantages in formulation development and manufacturing in addition to their therapeutic benefits[20]. Especially since pharmaceuticals with very low melting points require high temperatures and high processing pressures (such as drying granules and tablet compression), it is difficult to process pharmaceuticals at very low melting points, especially if they are liquid at ambient temperature, or if they convert to their own crystal state(e.g., granule drying and tablet compression). To stabilize drugs, a combination of drugs and lipids can be directly absorbed into solid particulate carriers. During the melting granulation process, lipid-based compounds can aid in the solubility and dispersion of medicines in solid solutions[21].

5. Solidification techniques for lipid-based systems

The following techniques can be used to process lipids to prepare solid oral lipid dosages forms such as pastilles, pellets, tablets, and capsules, also powders and granules, and others

5.1 Melt solidification technique [22, 23]

Melt solidification is a crucial process for producing the state liquid phase to the solid phase so that the products come out in a condition that is suitable during their transportation, storage, and subsequent use. This should be accomplished with the least amount of resources and the simplest, smallest amount of tools. The transformation of the melt material into a solid state with a certain kind and specific physical properties is a vital operation in the chemical and industrial industries.(Figure 1) The primary characteristic of solidification is crystallisation without separation.

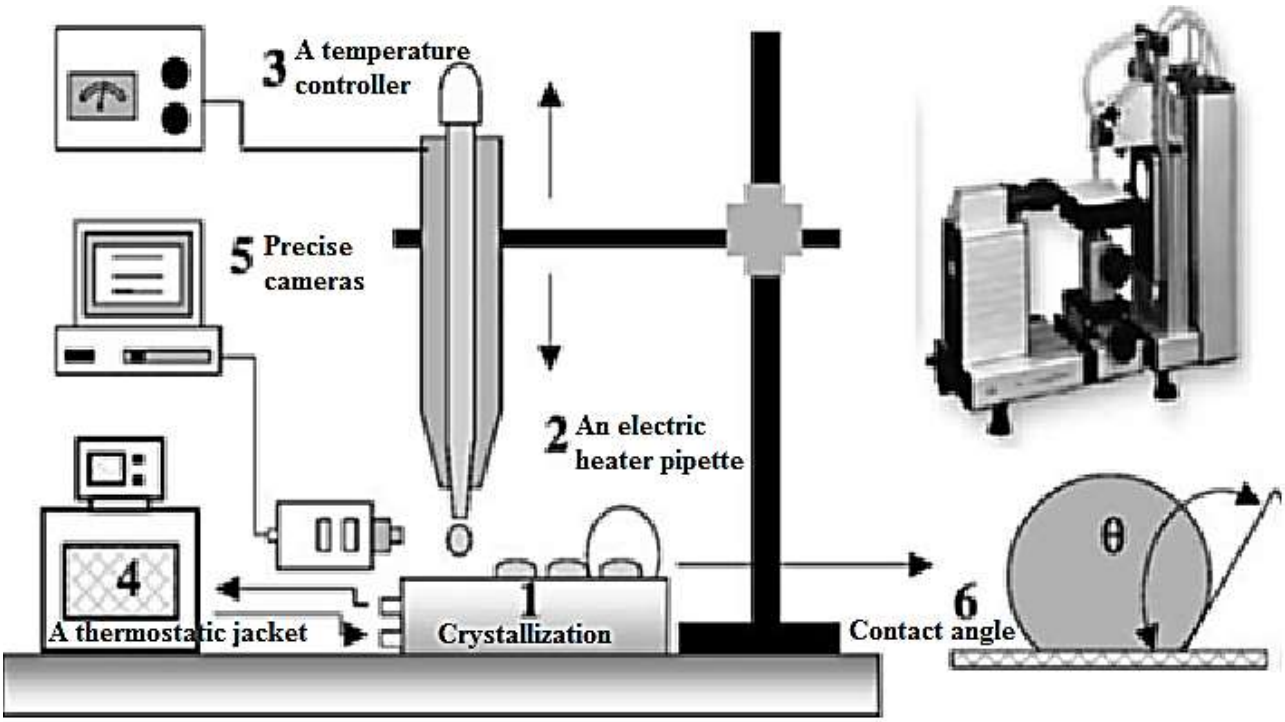

Figure 1: Diagram showing the configuration of the pastillation experimental setup[24]

Crystallization occurs under certain processes that affect the size, shape, crystal composition, hardness, and concentration of dust of solidified solids. Over the past decades, numerous solidification processes have been developed for the final size and shape of various standards. Pastillation is a method of rapidly converting melting into dispersed solids. The production of pastilles involves placing several drops on a cooled surface. The process of directly converting a liquid into a single-sized volume is called pastillation melts. Dust is not present during the pastillation process, which frequently occurs during the mechanical cutting and breaking process.

5.2 Dropping method

The dropping method, a novel technique for forming spherical particles from melted solid dispersions, helps various compounds crystallize. Round particles made using the dropping method can either be utilized as a ready dose form or put into capsules. If required, round particles might be treated further for coating. The production process is made simpler by using this approach instead of the other melt methods, which include pulverization, sifting, and compressibility issues.

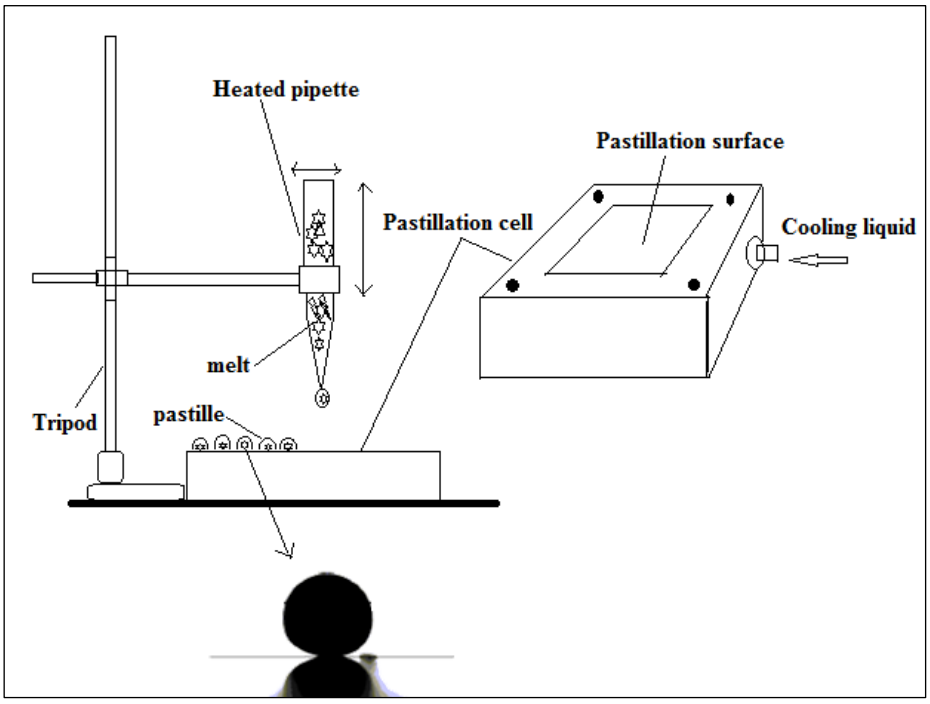

Figure 2: Graphical presentation of apparatus of dropping method with drops[25]

The dropping method is a brand-new technique for creating spherical particles from melted solid dispersions. Bülau and Ulrich created it to speed up the crystallization of various chemicals. Special tools created by Bülau and Ulrich were employed for this purpose (Figure 2). If a coating is preferred. The production process is made simpler by using this approach instead of the other melt methods, which include pulverization, sifting, and compressibility issues. Dropping is a green technology that doesn't use things that are bad for the environment.

5.3 Pastillation

The process of pastillation, which solidifies dusty, hazardous powder materials of chemicals into pastilles (hemi- spherical solidified units), is one that is frequently employed in the chemical, petrochemical, and agrochemical industries. This method makes it easier to handle the formed pastilles. Pastillation is the process of creating uniform-sized pastilles by depositing or allowing falling drops of chemical compounds to fall over a stainless steel surface that has been allowed to cool. The drops flatten slightly depending on their weight and the physical parameters of the melt, like viscosity and surface tension. The formed droplet then displays the traditional "pastille" shape. A particular piece of machinery called a "Rotoformer" is used to produce pastilles on a large scale. (Figure 3).

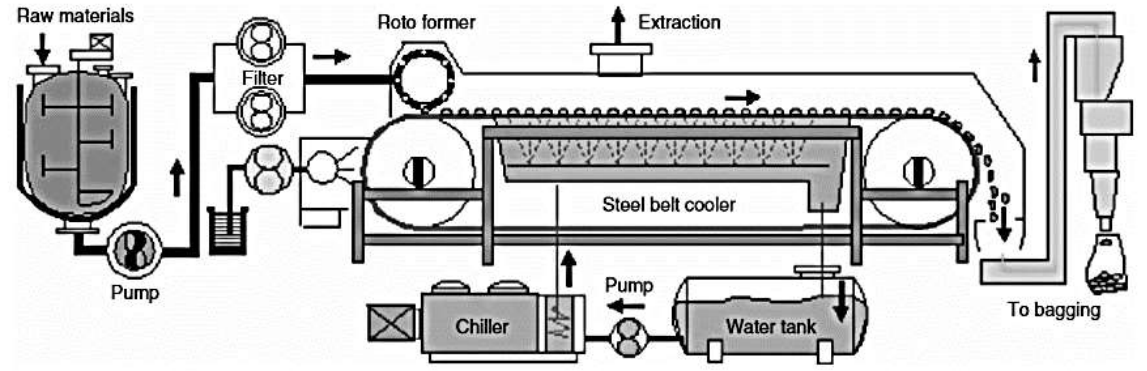

Figure 3: Schematic diagram of pastillation technique

5.4 Fabrication of melt solidification apparatus

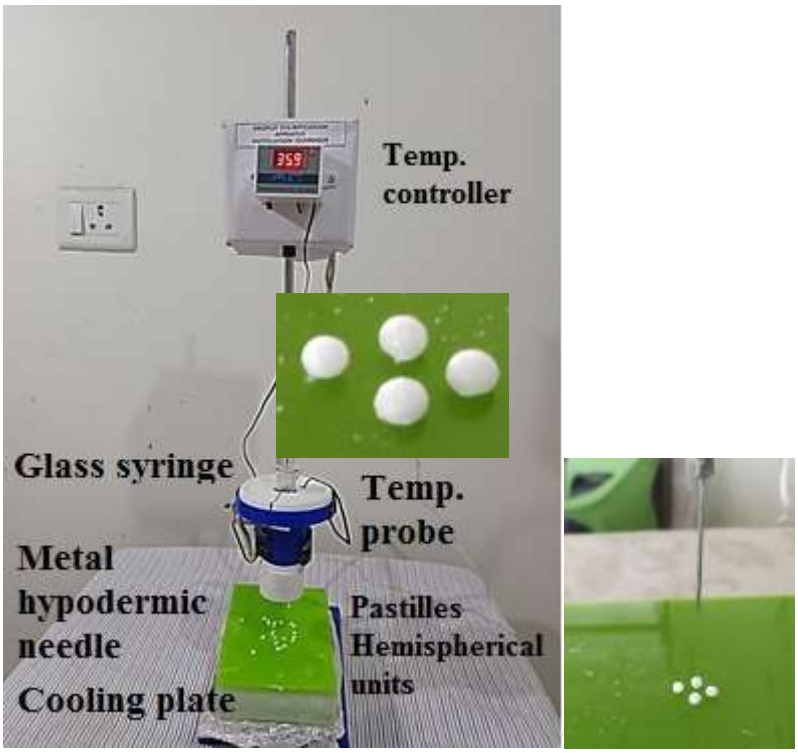

Figure 4: In house Labscale Melt solidification apparatus

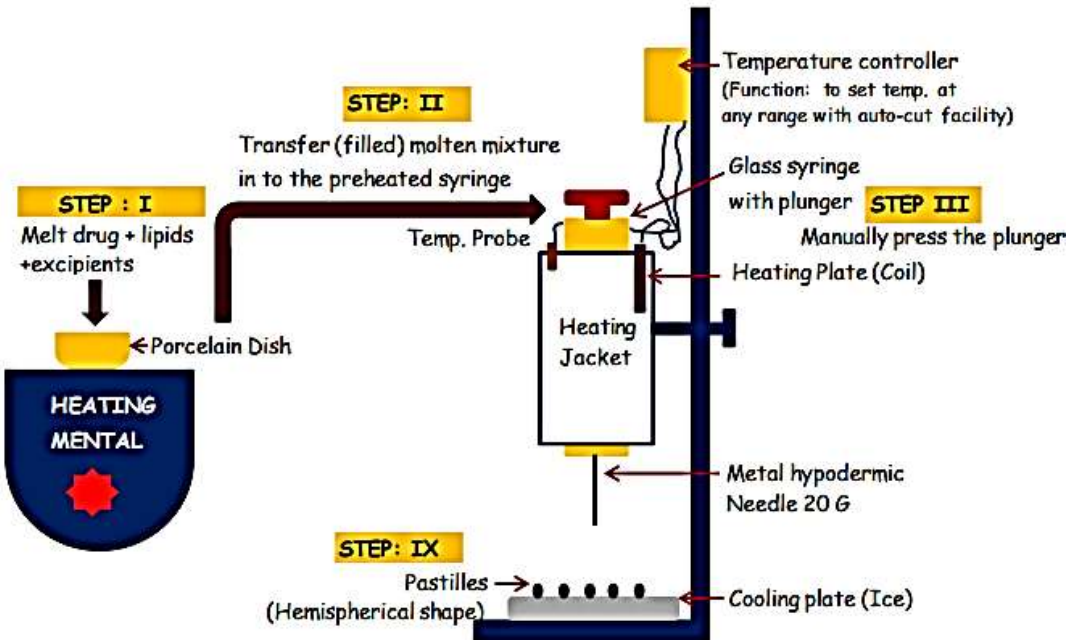

Figure 5: Stepwise procedure of pastilles formulation at laboratory level

Assembling and set up of pastilles formulation apparatus

In-house apparatus was developed to generate pastilles at the lab scale depicted in (Figure 4) The apparatus consists of a glass syringe or metal syringe with a plunger setup, hypodermic metal needles, and a heating coil on the outside of the glass syringe controlled by a temperature controller. The syringe was mounted on a burette holder, which was then set up on top of the metal plate. For cooling the base plate ice bag placed below the base plate. The droplet of molten material that fell onto the metallic plate was scraped off with the use of a sharp metal scraper after it had solidified and become known as the pastilles. The hardened pastilles were filled with '0' capsules of the specified size. The step wise process of pastilles formulation given in (Figure 5)

The roughness of the cooling surface, falling height, cooling rate, and crystallisation behaviour of the carrier are the main parameters involved in this process. Physical characteristics that are taken into account during processing include viscosity, surface tension, and melt density of the lipid.

Compared to other techniques for producing melt and solidify processes, this one has significant advantages. This method is suitable for processing of hygroscopic drugs and excipients the reason is this method not needed the organic solvents as well as this method also eliminates water during processing of ingredients. It is possible to produce the pastilles in a various sizes such as from 1 mm to 30 mm in diameter, are in solid spherical in shape, free-flowing, that are ideal for handling, filling, and packaging. When compared to powders, pastilles offer a larger bulk density as well as better packing capabilities.

A large amount of molten liquid is converted into discrete solidified units, resulting in a dust-free and solvent-free working environment. The entire procedure, which comprised melting fat, mixing the drug and essential excipients, and then solidifying, used only one piece of equipment. The absence of accompanying operations such as grinding, crushing, and other types of breaking processes reduces the pastillation process's energy cost. While larger pastilles may be strip-packed or poured immediately into sachets or bottles, smaller pastilles can be easily inserted to capsules.

5.5 Direct Compression[26]

Direct compression is just a two-step, simple, and continuous process that calls for mixing and lubricating powder materials before compaction. By cutting down on production costs and processing time, this approach may guarantee cost-effectiveness. Tablets are prepared through mixing API, a solid lipid and polymer agent, diluent, lubrication, and compressing the mixture in tablets. Lipids in smaller quantities than hydrophilic polymers may have a stronger retention effect, as their water-insolubleness reduces the penetration of liquids and, consequently, the dissolution and diffusion of drugs.

5.6 Granulation – Wet and Dry [27, 28]

Granulation is used to increase mix uniformity, compressibility, and powder flow characteristics. In addition to employing binder solutions and water also organic solvents, excipients such as lipid may also then granulated along with API in a dry form. Dry granulation creates thick granules using roller compaction, which, while less frequently used, is a continuous and energy-efficient technique that does not require solvents, which is beneficial for APIs that are hygroscopic or humidity-sensitive. Lipids can help hydrophilic matrices retain less water, resulting in medication release kinetics that are adequate. Because of their excellent binding qualities, hydrophilic polymers are typically used in wet granulation, which is a highly frequent technique in the pharmaceutical sector. These polymers, however, have a tendency to adhere in wet processing as well as cleaning when utilized in high quantities. Solid lipid excipients are substitute to the release rate retardant polymers used in wet granulation as they none swelling when in contact with liquids.

5.7 Melt Granulation/Melt Pelletization

Pelletization, also name for melt granulation, is a one-step, solvent-free method for producing formulations that sustained release and high drug loading requirements, as well as pharmaceuticals that cannot be freely water soluble[29]. The components get preblended using high-shear mixers as the temperature gradually rises to attain the lipid melting point. The lipids melt, causing the particles to bond to generate free-flowing granules[30]. An approach is to heat fatty excipients before adding them to a powder combination in a granulator

to create granules as well as pellets that may then be placed inside of capsules or crushed into tablets.[31] Melt-granulates enable a slower medication release over longer timespan than standard granulation methods. Drug loading, processability, and overall repeatability may all be improved by combining lipid excipients with various melting points[32].

5.9 Hot melt extrusion process [33, 34]

Hot melt extrusion is a continuous method that allows the creation of granules with extraordinarily high drug loadings (90-95%) without the need of solvents or protracted drying times. The conveying including kneading mechanism settings, temperature, or in-process controls are critical for improving process parameters or repeatability during extrusion. When lipid excipients are used as binders, drug bonding is promoted while dosage form wettability is reduced, resulting in a slower drug release. By remaining molecularly distributed within the molten lipid, the drug's solubility as well as release time may be improved. This method has the benefits of being simple, scalable, and versatile enough to provide a wide range of dose forms.

5.10 Molding[35]

The easiest method for creating lipid-based continuous medication delivery systems is molding. Before being put into ethyl cellulose cylinders, capsules, or cast into molds to make tablets, the drug is dissolved in the lipid melt. An insoluble, hydrophobic lipid excipient is created as an extremely dense, pore less, hydrophobic, and poorly wettable matrix. Mannitol and polyethylene glycols are examples of hydrophilic pore formers that can be employed to make these dosage forms more wettable. Despite being simple to use, this approach is over followed by the acceptability as well as popularity of the usual compressed tablet forms.

5.11 Spray Congealing Method or Chilling and Prilling Method[36]

Drug microparticles are produced by processes such as spray congealing or prilling and then incorporated into the lipid matrix. When the lipid has completely melted, the drug will get dissolved or finely dispersed. After being atomized with a pneumatic nozzle in a cool chamber, this mixture is next dried. The method is not appropriate for formulations that are extremely drug-loaded because overly viscous mixes can result in nozzle obstruction, and irregularly shaped, or excessively large particles.

5.12 Hot-Melt Coating[37]

Hot-melt coating eliminates the need for solvents by spraying molten lipid excipients on the surface of the medicine to create a lipid coating. The medicine can then be compacted into tablets or placed into capsules after being coated. The method is quicker and less expensive than traditional coating procedures, which calls for the expensive, tiresome, and time-consuming evaporation and/or recovery of solvent. Drawbacks include processing thermo-labile chemicals and a small selection of excipients.

The processing adaptability of lipid excipients is provided in (Table 2) for the production of sustained release dose.

Table 1: Properties of drug, dose and related process[38]

Characteristics of Drug	Related Process	Classes of Release Modifiers/fillers
Drugs that are water insoluble	Effective techniques include dry/wet granulation and direct compression.	Diluents that are water-insoluble are best suited Surfactants for stabilization Polymers that are water soluble are best suited Disintegrating agents
Drugs that are water soluble	The following methods are appropriate: direct extrusion, melt extrusion, wet/alloy granulation, spray solidification, hot melt coating.	Diluents that are water-insoluble are best suited. Additionally, hydrophobic and hydrophilic swelling polymers are employed.
A drug that has low therapeutic dose	Melt and then mix capsule moulding and direct compression are suitable techniques.	Diluents that are hydrophilic polymers get swell when exposed to water, surfactants, sugars, and disintegrants
Drugs that have a high therapeutic dose	The best method is hot melt coating, which is followed by capsule moulding, melt extrusion, dry granulation, and wet granulation also the melt granulation.	Non-water soluble appropriately flowing and compressible Fillers and diluents
Drugs that are hygroscopic (water sensitive) in nature	It is appropriate to use the hot melt extrusion, direct compression, hot melt coating, spray cooling, dry/melt granulation, and capsule moulding techniques.	Choice of diluents and fillers are non-hygroscopic
A drug that is thermo-labile (heat sensitive)	The appropriate method is Direct compression Wet granulation	All

6. Drug release mechanism from lipid matrices

Understanding the main release of drugs mechanism in depth is essential for proper product development as well as drug safety. However, little is known about how drugs are released from lipid-based preparations[39]. There are numerous durable polymer-based drug delivery technologies that have undergone thorough analysis.

7. Mechanism by which drug releases sustained manner from lipid matrices

Solid dosage forms produced using insoluble lipid excipients have been shown to maintain their integrity during drug release without dissolving or gelling[40]. This shows a pure Fickian diffusion mechanism that involves (a) water permeates the matrix's interior, (b) the get drug dissolves, (b) takes up pores resulting from the diffusion of dissolved drug particles, (c) generates water-filled channels thereby enhancing matrix porosity as well as drug mobility, and (v) ensures constant drug diffusion from the dosage form into the drug release medium. The importance of water diffusion into the device can be inferred from the aforementioned release mechanism, which assumes that the lipid matrix fully attempts to keep its geometric structure upon dissolution while drug release is based solely on Fickian diffusion. Such lipid matrices' rate-limiting component for release. This is due to the fact that water in the matrix alone has the ability to dissolve drugs and form tiny pores for drug diffusion. As a result, lipids and pharmacological qualities have a significant impact on the matrix wettability's characteristics. Some solid lipids and process used for formulation listed in (Table 3).

Table 2: Solid lipid materials used to sustain the release of dosage forms[41-44].

Lipids class	Chemical configuration	Characteristics	Examples	Process
Waxy materials	Fatty acid esters and long chain alcohol	Water insoluble nature Melting point range 62-86°C	Solid paraffin, candelilla wax, carnauba wax, and beeswax Cetyl palmitate	Cold, hot
Oils from Vegetable origin	combination of phospholipids, triglycerides, and free fatty acids	Digestible Melting Point: 60-71°C	hydrogenated soyabean oil, castor oil, and cottonseed oil	Cold, hot
Polyoxyl glycerides	combination of polyethylene glycols, glycerides, and fatty acid esters	In part digestible 50°C for melting	Stearoyl polyoxyl-32, Stearoyl polyoxyl-6, and glycerides	hot
Triglycerides and fatty acids	Long chain fatty acids, triglycerides and monoacids Triglycerides, monoacids	Melting Point: 60-90°C Melting Point: 46-73°C	Behenic acid, Stearic acid, Palmitic acid, Glyceryl tripalmitate and tristearate	Hot and Cold
Partially glycerides	mono-, di-, and triglyceride mixtures	Melting Point: 54°C -74°C	Glyceryl behenate, distearic acid, and monoesters of glyceryl	Hot and Cold
Fatty alcohol	fatty alcohol mixture	Melting Point : 48°C -56°C	Alcohols from cetyl and cetostearyl	Hot and Cold

8. Drug release adjustment

To obtain the desired drug release, formulation factors might be considered in addition to how dosage form dimensions and compression forces affect matrix porosity and diffusion channel length. It has been shown that the potency of lipid-based dosage forms depends on the kind of drugs, the lipids, and the manufacturing procedures. The molding and spray congealing of insoluble lipids create a very incomprehensible system that releases extremely slow drugs so a very long period of time, but the compression of a physical powder mixture makes it easy for water to spread into the device. The inclusion of other components may be used to control and optimize the drug released from the lipid matrix[45, 46]. This modulation is caused by facilitation or inhibition of water input to the matrix. These soluble chemicals dissolve immediately when they meet the release medium, and then the drugs quickly diffuse from the matrix through the hole and water channel they create. The hydrophilic fillers such as mannitol and lactose dissolved very quickly in water media, forming these channels in matrix. When high water-soluble drugs or high drug concentrations are diluted with calcium phosphate in low-water rather than lactose or mannitol, the drug release rate may be significantly increased[47-50]. Pores can be made from hydrophilic surfactants, polymers, or other chemicals that perform the same role as hydrophilic diluents in to the tablet formulations[51]. Once exposed to the release media, the pores that form expand or leak out from the lipid matrix, increasing the amount of medication released[52-54]. Poloxamers have been added into the glyceryl distearate matrix formed via capsule molding. Drug release increased by the incorporation of increasing amounts of hydrophilic polymers, allowing control and optimization of drug release rates.

9. Benefits of multiparticulate system and its application

A multiparticulate system is a matrix or reservoir that contains a large number of small drug depots or drug release units. Multiparticulate are defined as a single administrable dose of a drug that is uniformly dispersed among numerous smaller units of a specific uniform size and dimension ranging from the nano- to the mill scale. The term "multiparticulate" means distinct, small, repeating drug particles that may or may not follow a similar pattern of drug release. It is also known as "multiple unit dose forms."

Depending on the polymer used in the manufacturing process, they can be made for delayed, pulsatile, controlled, or targeted drug release. They can be made by combining excipients or drug material into fine powders or granules with the proper processing equipment as well as technology. Pharmaceutical technology has previously noticed the full potential for this approach because of the adaptability in product development as well as design and excellent flow properties due to uniformity in size as well as sphere-shaped agglomerates, higher physical stability, excellent strength, low friability, narrowed distribution of particle sizes, excellent quality throughout coating application, compatible packing characteristics, along with therapeutic advantages it provides

[55,56]. The best thing about multiparticulate systems is that the desirable dose units may be easily removed from them without modifying the formulation or manufacturing process, which has little to no influence on the relative amount of medication released. Depending on its surface area, every modified release dosage form having varying strengths releases drug in a different way. Identical to matrix-sustained release tablets, the surface area change that occurs with a change in tablet form is often not proportionate to the dosage strength, resulting in various drug release patterns.

10. Modified drug delivery system

The most reliable and frequently used dose forms are oral solid dosage forms. Tablets have been widely used since the latter half of the nineteenth century, and their appeal has not diminished. Because of the benefits offered to both pharmaceutical makers and patients, tablets are still a common dosage form. They include straightforward preparation and cost-effective packaging, precision of a single dosing regimen, portability and compactness, as well as administration simplicity and blandness, are all advantages of the drug manufacturing methods.

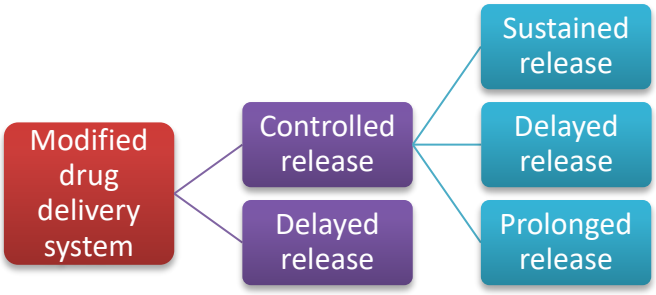

Figure 6: Categories of modified drug delivery system

Modified release dosage forms differ than immediate release dosage form by the fact that the substances that constitute the active ingredient are released at a different pace and/or place. This purposeful alteration is produced via unique formulation design as well as. This recommendation covers oral, intramuscular, subcutaneous, and transdermal delivery of modified release dosage forms. Many technological advances that have attempted to address the shortcomings of traditional drug delivery methods have resulted in the creation of modified release drug delivery systems[57, 58]. Different categories can be easily created from the changed release distribution systems (Figure 6).

11. Rationale for developing dosage formulations with controlled or sustained releases

Pharmaceuticals intended for oral administration often use traditional drug delivery systems that are intended for instant drug release for quick/immediate absorption. The drug level in the blood is not kept at a constant level when the standard dosage form is administered extravascularly. Due to the typical dosage form's inability to regulate temporal administration, the duration of effect is short[59]. The requirement for repeated administration of drugs with a half-life, which raises the risk of forgetting to take a dose and reduces patient compliance, is one disadvantage of the conventional dosage forms, which include solution, suspension, tablet, capsule, as well as suppository[60,61].

1. The typical peak-valley plasma concentration-time profile (Figure 7) makes it difficult to reach a steady state. The inherent drug concentration changes may cause undermedicating or overmedicating as the steady state concentration values decrease or increase outside of the therapeutic range.
2. When there is an overdose, the variable drug levels may have undesirable consequences, particularly for a substance with a low therapeutic index.
3. Controlled drug delivery systems, which have the potential to totally revolutionise the administration of medication and provide a variety of therapeutic advantages, have emerged in response to the drawbacks of conventional drug delivery systems.

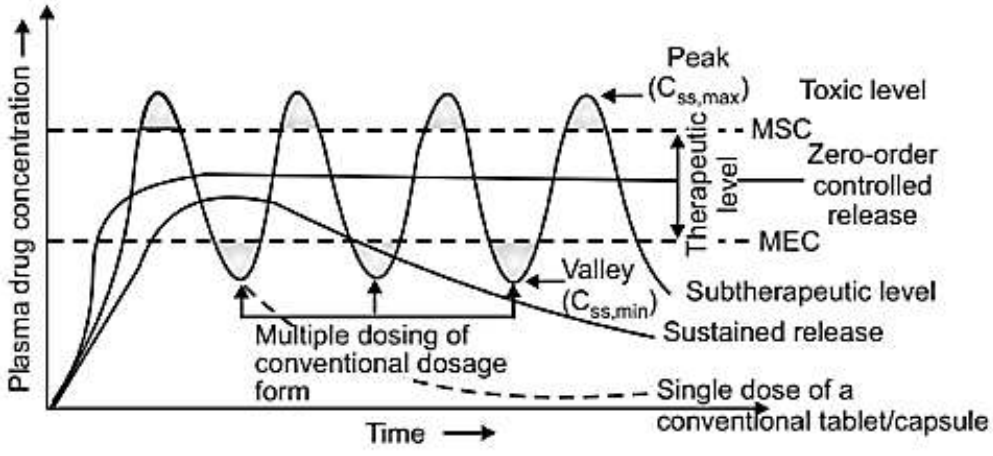

Figure 7: Graphical representation of plasma drug concentration profiles for different released mechanisms of formulations[62]

New and creative drug delivery techniques have quickly replaced traditional drug dose forms during the past few years. The controlled release/sustained release dosage formulations are widely used in modern medicines. Controlled drug delivery mainly tries to change the physiological and/or molecular properties inherent in a specific route of administration in order to impact the pharmacokinetic as well as pharmacodynamics features of pharmacologically active components.

12. Conclusion

The rapidly expanding pharmaceutical sector is constantly seeking out new active compounds, which eventually calls for an appropriate dosage form capable of efficiently delivering those molecules in the body. The production of oral formulations can use a variety of excipients, but lipids have the added benefit of increasing the bioavailability of medications that are highly metabolised and lipophilic. The use of specific lipid excipients in formulations for sustained release is primarily justified by their hydrophobicity and inertness, which allow the creation of matrixes that effectively delay release. They have fascinating biopharmaceutical features in addition to performance that is equivalent to polymer-based matrices. Therefore, a focus on innovation, advancement, and solving issues related to lipid-based manufacturing technology should be given. Additionally, where other methods are constrained due to intellectual property restrictions, new dosage forms like pastilles, solid SMEDDS, and new technologies like freeze-pelletization may be employed to improve the therapeutic efficacy of some medications. Additionally, using lipids as the main excipient might assist reduce the dosage of the medicine, particularly those with a low water solubility. Therefore, such efforts of formulation scientists will considerably improve the current healthcare system and assist patients in leading healthier lives.

Conflict of Interest: None

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References

1) Stuchlík M, Zak S. Lipid-based vehicle for oral drug delivery. Biomedical Papers-Palacky University in Olomouc. 2001 Dec 1; 145(2):17-26. https://doi.org/10.5507/bp.2001.008

2) Stegemann S, Leveiller F, Franchi D, De Jong H, Lindén H. When poor solubility becomes an issue: from early stage to proof of concept. European journal of pharmaceutical sciences. 2007 Aug 1; 31(5):249-61. https://doi.org/10.1016/j.ejps.2007.05.110

3) Chakraborty S, Shukla D, Mishra B, Singh S. Lipid-an emerging platform for oral delivery of drugs with poor bioavailability. European journal of pharmaceutics and biopharmaceutics. 2009 Sep 1; 73(1):1-5. https://doi.org/10.1016/j.ejpb.2009.06.001

4) Drewe JU, Meier RE, Vonderscher JA, Kiss DE, Posanski UL, Kissel T, Gyr K. Enhancement of the oral absorption of cyclosporin in man. British journal of clinical pharmacology. 1992 Jul; 34(1):60-4. https://doi.org/10.1111/j.1365-2125.1992.tb04108.x

5) Kovarik JM, Mueller EA, Kutz K, Van Bree JB, Tetzloff W. Reduced inter-and intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. Journal of pharmaceutical sciences. 1994 Mar 1; 83(3):444-6. https://doi.org/10.1002/jps.2600830336

6) Odeberg JM, Kaufmann P, Kroon KG, Höglund P. Lipid drug delivery and rational formulation design for lipophilic drugs with low oral bioavailability, applied to cyclosporine. European journal of pharmaceutical sciences. 2003 Dec 1; 20(4-5):375-82. https://doi.org/10.1016/j.ejps.2003.08.005

7) Porter CJ, Charman WN. Intestinal lymphatic drug transport: an update. Advanced drug delivery reviews. 2001 Aug 23; 50(1-2):61-80. https://doi.org/10.1016/S0169-409X(01)00151-X

8) Prabhu S, Ortega M, Ma C. Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. International journal of pharmaceutics. 2005 Sep 14; 301(1-2):209-16. https://doi.org/10.1016/j.ijpharm.2005.05.032

9) Kim JW, Ulrich J. Prediction of degree of deformation and crystallization time of molten droplets in pastillation process. International journal of pharmaceutics. 2003 May 12; 257(1-2):205-15. https://doi.org/10.1016/S0378-5173(03)00141-8

10) Zurao P, Landge S, Jaiswal S, Chandewar A. Lipids-The instrumental excipient in pharmaceutical dosages form. International Journal of Research in Pharmacy and Chemistry. 2011; 1(4):992-7.

11) Gülmezoğlu E, Yıldız Türkyılmaz G, Karasulu HY. Preparation and Evaluation of a Lipid-Based Drug Delivery System to Improve Valsartan Oral Bioavailability: Pharmacokinetic and Pharmacodynamic Analysis. Drug Development and Industrial Pharmacy. 2022 Dec 30(just-accepted):1-5. https://doi.org/10.1080/03639045.2022.2164588

12) Rosiaux Y, Jannin V, Hughes S, Marchaud D. Solid lipid excipients-Matrix agents for sustained drug delivery. Journal of Controlled Release. 2014 Aug 28; 188:18-30. https://doi.org/10.1016/j.jconrel.2014.06.004

13) Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems-an overview. Acta Pharmaceutica Sinica B. 2013 Dec 1; 3(6):361-72. https://doi.org/10.1016/j.apsb.2013.10.001

14) Zaro JL. Lipid-based drug carriers for prodrugs to enhance drug delivery. The AAPS journal. 2015 Jan; 17:83-92. https://doi.org/10.1208/s12248-014-9670-z

15) Garrigue JS, Lambert G, Benita S. Self-emulsifying oral lipidbased formulations for improved delivery of lipophilic drugs. Microencapsulation: Methods and Industrial Applications. 2006; 2:429-80. https://doi.org/10.1201/9781420027990.pt3

16) Puri A, Loomis K, Smith B, Lee JH, Yavlovich A, Heldman E, Blumenthal R. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2009; 26(6). https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v26.i6.10

17) Pardeshi C, Rajput P, Belgamwar V, Tekade A, Patil G, Chaudhary K, Sonje A. Solid lipid based nanocarriers: An overview/Nanonosači na bazi čvrstih lipida: Pregled. Acta pharmaceutica. 2012; 62(4):433-72. https://doi.org/10.2478/v10007-012-0040-z

18) Elmowafy M, Al-Sanea MM. Nanostructured lipid carriers (NLCs) as drug delivery platform: Advances in formulation and delivery strategies. Saudi Pharmaceutical Journal. 2021 Sep 1; 29(9):999-1012. https://doi.org/10.1016/j.jsps.2021.07.015

19) Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022 Feb 17; 27(4):1372. https://doi.org/10.3390/molecules27041372

20) Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, Rosenholm JM. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics. 2018 Oct 18; 10(4):191. https://doi.org/10.3390/pharmaceutics10040191

21) Konermann L, Pan J, Liu YH. Hydrogen exchange mass spectrometry for studying protein structure and dynamics. Chemical Society Reviews. 2011; 40(3):1224-34. https://doi.org/10.1039/C0CS00113A

22) Siram K, Rahman SH, Balakumar K, Duganath N, Chandrasekar R, Hariprasad R. Pharmaceutical nanotechnology: brief perspective on lipid drug delivery and its current scenario. In Biomedical applications of nanoparticles 2019 Jan 1 (pp. 91-115). William Andrew Publishing. https://doi.org/10.1016/B978-0-12-816506-5.00005-X

23) Becker K, Salar-Behzadi S, Zimmer A. Solvent-free melting techniques for the preparation of lipid-based solid oral formulations. Pharmaceutical Research. 2015 May; 32:1519-45. https://doi.org/10.1007/s11095-015-1661-y

24) Kim JW, Ulrich J. Prediction of degree of deformation and crystallization time of molten droplets in pastillation process. Int J Pharm. 2003 May 12; 257(1-2):205-15. PMID: 12711175. https://doi.org/10.1016/S0378-5173(03)00141-8

25) Bashiri-Shahroodi A, Nassab PR, Szabó-Révész P, Rajkó R. Preparation of a solid dispersion by a dropping methodto improve the rate of dissolution of meloxicam. Drug development and

industrial pharmacy. 2008 Jan 1; 34(7):781-8. https://doi.org/10.1080/03639040801925735

26) Mohamed FA, Roberts M, Seton L, Ford JL, Levina M, Rajabi-Siahboomi AR. The influence of HPMC concentration on release of theophylline or hydrocortisone from extended release mini-tablets. Drug Development and Industrial Pharmacy. 2013 Aug 1; 39(8):1167-74. https://doi.org/10.3109/03639045.2012.681053

27) Rosiaux Y, Jannin V, Hughes S, Marchaud D. Solid lipid excipients-Matrix agents for sustained drug delivery. Journal of Controlled Release. 2014 Aug 28; 188:18-30. https://doi.org/10.1016/j.jconrel.2014.06.004

28) Jamzad S. Analysis and application of bio-erodible swelling polymers in the development of controlled-release matrix systems for low-dose BCS class 2 drugs, using glipizide as a model drug. Temple University; 2006.

29) Wang B, Sun X, Xiang J, Guo X, Cheng Z, Liu W, Tan S. A critical review on granulation of pharmaceuticals and excipients: Principle, analysis and typical applications. Powder Technology. 2022 Mar 30:117329. https://doi.org/10.1016/j.powtec.2022.117329

30) Dash TR, Verma P. Matrix tablets: an approach towards oral extended release drug delivery. International Journal of Pharma Research & Review. 2013 Feb; 2(2):12-24.

31) Kowalski J, Kalb O, Joshi YM, Serajuddin AT. Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product. International journal of pharmaceutics. 2009 Oct 20; 381(1):56-61. https://doi.org/10.1016/j.ijpharm.2009.05.043

32) Sirisha VR, Sri KV, Suresh K, Reddy GK, Devanna N. A review of pellets and pelletization process-A multiparticulate drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2013 Jun 1; 4(6):2145.

33) Bose S, Bogner RH. Solventless pharmaceutical coating processes: a review. Pharmaceutical development and technology. 2007 Jan 1; 12(2):115-31. https://doi.org/10.1080/10837450701212479

34) Damian F, Harati M, Schwartzenhauer J, Van Cauwenberghe O, Wettig SD. Challenges of dissolution methods development for soft gelatin capsules. Pharmaceutics. 2021 Feb 4; 13(2):214. https://doi.org/10.3390/pharmaceutics13020214

35) Tran PH, Tran TT, Park JB, Lee BJ. Controlled release systems containing solid dispersions: strategies and mechanisms. Pharmaceutical research. 2011 Oct; 28:2353-78. https://doi.org/10.1007/s11095-011-0449-y

36) Vasanthavada M, Serajuddin AT. Lipid-based self-emulsifying solid dispersions. InOral Lipid-Based Formulations 2007 Jun 8 (pp. 171-206). CRC Press. https://doi.org/10.3109/9781420017267-10

37) Osmałek T, Froelich A, Jadach B, Tatarek A, Gadziński P, Falana A, et al. Recent Advances in Polymer-Based Vaginal Drug Delivery Systems. Pharmaceutics [Internet] 2021; 13(6):884. https://doi.org/10.3390/pharmaceutics13060884

38) Freire Petrovick G. Orodispersible Tablets Containing Taste-Masked Lipid Pellets with Metformin Hydrochloride for Use by Elderly Patients (Doctoral dissertation, Düsseldorf, Heinrich-Heine-Universität, Diss., 2015).

39) Jannin V, Cuppok Y. Hot-melt coating with lipid excipients. International journal of pharmaceutics. 2013 Dec 5; 457(2):480-7. https://doi.org/10.1016/j.ijpharm.2012.10.026

40) Zaid Alkilani A, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015 Oct 22; 7(4):438-70. https://doi.org/10.3390/pharmaceutics7040438

41) Tan A, Rao S, Prestidge CA. Transforming lipid-based oral drug delivery systems into solid dosage forms: an overview of solid carriers, physicochemical properties, and biopharmaceutical performance. Pharmaceutical research. 2013 Dec; 30:2993-3017. https://doi.org/10.1007/s11095-013-1107-3

42) Kolbina M. Phospholipids as functional excipients in solid oral dosage forms. Freie Universitaet Berlin (Germany); 2018.

43) Steward PA, Hearn J, Wilkinson MC. An overview of polymer latex film formation and properties. Advances in colloid and interface science. 2000 Jul 28; 86(3):195-267. https://doi.org/10.1016/S0001-8686(99)00037-8

44) Kreye F, Siepmann F, Siepmann J. Drug release mechanisms of compressed lipid implants. International journal of pharmaceutics. 2011 Feb 14; 404(1-2):27-35. https://doi.org/10.1016/j.ijpharm.2010.10.048

45) Güres S, Siepmann F, Siepmann J, Kleinebudde P. Drug release from extruded solid lipid matrices: theoretical predictions and independent experiments. European journal of pharmaceutics and biopharmaceutics. 2012 Jan 1; 80(1):122-9. https://doi.org/10.1016/j.ejpb.2011.10.002

46) Guse C, Koennings S, Kreye F, Siepmann F, Göpferich A, Siepmann J. Drug release from lipid-based implants: elucidation of the underlying mass transport mechanisms. International journal of pharmaceutics. 2006 May 18; 314(2):137-44. https://doi.org/10.1016/j.ijpharm.2005.08.030

47) Rosiaux Y, Jannin V, Hughes S, Marchaud D. Solid lipid excipients-Matrix agents for sustained drug delivery. Journal of Controlled Release. 2014 Aug 28; 188:18-30. https://doi.org/10.1016/j.jconrel.2014.06.004

48) Schulze S, Winter G. Lipid extrudates as novel sustained release systems for pharmaceutical proteins. Journal of Controlled Release. 2009 Mar 19; 134(3):177-85. https://doi.org/10.1016/j.jconrel.2008.11.026

49) Treanor G, Roberts M, Mostafa S, Miolane C. Diluent Effects on Drug Release from Sustained-Release Compritol (R) 888 ATO Tablets. InJournal of Pharmacy and Pharmacology 2010 Oct 1 (Vol. 62, No. 10, pp. 1419-1420).

50) Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2001 Sep 1; 52(2):181-90. https://doi.org/10.1016/S0939-6411(01)00162-X

51) El-Shanawany S. Sustained release of nitrofurantoin from inert wax matrixes. Journal of controlled release. 1993 Jul 1; 26(1):11-9. https://doi.org/10.1016/0168-3659(93)90204-I

52) Herrmann S, Winter G, Mohl S, Siepmann F, Siepmann J. Mechanisms controlling protein release from lipidic implants: effects of PEG addition. Journal of controlled release. 2007 Apr 2; 118(2):161-8. https://doi.org/10.1016/j.jconrel.2006.11.001

53) Sax GL. Twin-screw extruded lipid implants for controlled drug delivery (Doctoral dissertation, lmu).

54) Jannin V, Pochard E, Chambin O. Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing Precirol® ATO 5. International journal of pharmaceutics. 2006 Feb 17; 309(1-2):6-15. https://doi.org/10.1016/j.ijpharm.2005.10.042

55) Mohl S, Winter G. Continuous release of rh-interferon α-2a from triglyceride matrices. Journal of controlled release. 2004 May 31; 97(1):67-78. https://doi.org/10.1016/j.jconrel.2004.02.027

56) Güres S, Kleinebudde P. Dissolution from solid lipid extrudates containing release modifiers. International journal of pharmaceutics. 2011 Jun 30; 412(1-2):77-84. https://doi.org/10.1016/j.ijpharm.2011.04.010

57) Jannin V, Bérard V, Andrès C. Modification of the drug release of ibuprofen by Hot-Melt Coating with mixes of Compritol® 888 ATO and non-ionic surfactants. Tablet. 2005; 80(90):100.

58) Goodhart FW, McCoy RH, Ninger FC. Release of a water-soluble drug from a wax matrix timed-release tablet. Journal of Pharmaceutical sciences. 1974 Nov 1; 63(11):1748-51. https://doi.org/10.1002/jps.2600631117

59) Schwartz JB, Simonelli AP, Higuchi WI. Drug Release from Wax Matrices II: Application of a Mixture Theory to the Sulfanilamide-

Wax System. Journal of Pharmaceutical Sciences. 1968 Feb 1; 57(2):278-82. https://doi.org/10.1002/jps.2600570207

60) Ratsimbazafy V, Bourret E, Brossard C. Influence of the manufacturing process on the release of proxyphylline from lipid matrices. Pharmazie. 1997; 52(11):863-6.

61) Özyazıcı M, Gökçe EH, Ertan G. Release and diffusional modeling of metronidazole lipid matrices. European journal of pharmaceutics and biopharmaceutics. 2006 Jul 1; 63(3):331-9. https://doi.org/10.1016/j.ejpb.2006.02.005

62) Kreye F, Siepmann F, Siepmann J. Drug release mechanisms of compressed lipid implants. International journal of pharmaceutics. 2011 Feb 14; 404(1-2):27-35. https://doi.org/10.1016/j.ijpharm.2010.10.048