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Effect of Lubricants and Lubrication Time on the Release of Granules for Compaction: A Comprehensive Review of Mechanisms, Formulation Variables and Evaluation

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Abstract- ***Lubricants are indispensable yet paradoxical excipients in tablet manufacture: present at concentrations of only a fraction of a percent to a few percent, they reduce die-wall friction, prevent sticking and improve granule flow, but the very surface activity that makes them effective can also impair the mechanical strength, disintegration and dissolution of the finished tablet. This review examines how the type of lubricant and the duration of lubrication (mixing) time together govern the compaction behaviour and drug-release performance of granules, taking paracetamol—a poorly compressible, poorly flowing model drug manufactured almost exclusively by wet granulation—as the reference system. Five representative lubricants are compared: the hydrophobic stearates (stearic acid, magnesium stearate and zinc stearate) and the more hydrophilic sodium benzoate and polyethylene glycol. The mechanism of boundary lubrication, the well-documented "magnesium stearate effect" and the phenomenon of over-lubrication on prolonged mixing are discussed in detail, alongside the influence of lubricant type and lubrication time on granule flowability (Carr's index and Hausner ratio), tablet hardness, disintegration time and in-vitro dissolution and its kinetics. Illustrative analytical data, a complete evaluation framework and current market context are presented graphically. Hydrophilic lubricants and shorter, well-controlled lubrication times generally favour faster release, whereas hydrophobic stearates and prolonged mixing slow disintegration and dissolution; the central conclusion is that lubricant selection and lubrication time must be jointly optimised—ideally through a statistically designed approach—to balance manufacturability against drug release.***

Keywords: Lubricant, Lubrication Time, Magnesium Stearate, Over-Lubrication, Tablet Compaction, Granule Flowability, Dissolution, Paracetamol, Wet Granulation.

I. INTRODUCTION

The compressed tablet remains the most widely produced and most widely consumed pharmaceutical dosage form, prized for its dosing accuracy, physical and chemical stability, ease of handling, patient convenience and economy of large-scale manufacture. Global tablet output is enormous—exceeding an estimated 2.8 trillion units in a single recent year—and the reliable production of tablets of consistent weight, strength and drug-release behaviour depends on the careful selection and processing of a small number of functional excipients [14]. Among these, the lubricant occupies a uniquely influential position: although typically incorporated at only 0.25 to 5% by weight, it exerts effects on the final product out of all proportion to its quantity.

Granulation, the process of binding fine primary particles into larger, free-flowing granules, is a central step in the manufacture of most tablets, improving the handling, flow and compressibility of the powder blend and ensuring uniform die filling and content uniformity. Lubrication, generally performed as the final blending step after the granules have been dried and sized, serves three related purposes: it reduces friction between the powder bed and the metal surfaces of the punches and die, it prevents the blend from adhering to the tooling, and it improves the flow of granules into the die cavity. Without adequate lubrication, tablets stick to the punches, eject with difficulty, exhibit weight variation and damage the tooling [4, 9].

Yet lubrication is a double-edged process. The most effective lubricants are hydrophobic, fine, laminar materials—magnesium stearate being the archetype—

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that spread readily over the surfaces of granules to form a low-friction film. The same film, however, interposes a water-repellent, weakly bonding layer between particles, and so can reduce the tensile strength of the resulting tablet and retard the penetration of dissolution medium, prolonging disintegration and slowing drug release. The magnitude of these effects depends not only on the chemical nature and quantity of the lubricant but, critically, on the lubrication time—the duration for which the lubricant is mixed with the granules—because mixing controls how completely the lubricant film is distributed and developed over the granule surfaces [82, 83].

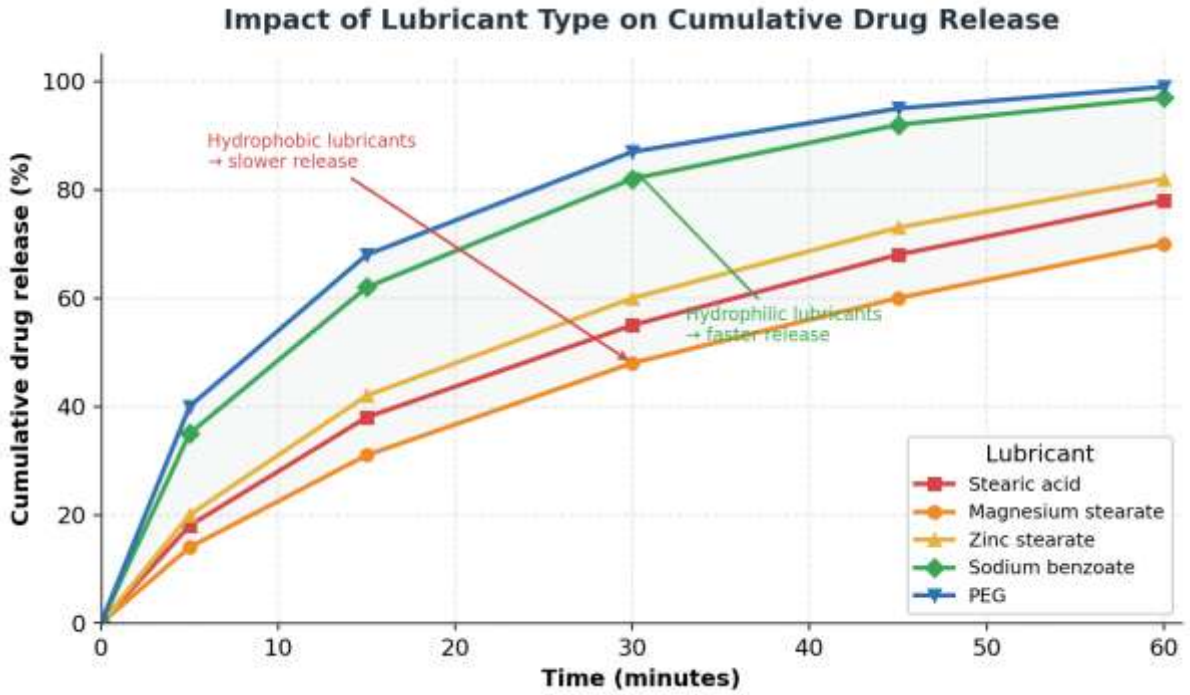

Figure 1. Illustrative impact of lubricant type on the cumulative drug-release profile of compressed granules. Hydrophobic stearates retard release, whereas the more hydrophilic sodium benzoate and polyethylene glycol promote faster, more complete release.

This review addresses the combined influence of lubricant type and lubrication time on the compaction and release behaviour of granules, using paracetamol (acetaminophen) as a model drug. Five representative lubricants of differing hydrophilicity—stearic acid, magnesium stearate, zinc stearate, sodium benzoate and polyethylene glycol—are compared (Figure 1). The mechanism of pharmaceutical lubrication, the classes and properties of common lubricants, the phenomenon of over-lubrication, the effects on flowability, hardness, disintegration and dissolution, and the analytical framework by which these are assessed are examined in turn, with illustrative data presented throughout. An understanding of these relationships is essential to the rational design of robust, high-quality tablet formulations that balance efficient manufacture against the desired therapeutic release profile.

II. THE ROLE AND MECHANISM OF LUBRICATION IN TABLETING

In tablet manufacture three distinct but often conflated functions are served by so-called lubricants. True lubricants reduce friction between the tablet and the die wall during compression and ejection; anti-adherents prevent the adhesion of the powder to the faces of the punches; and glidants improve the flow of the granules by reducing interparticulate friction. Many materials display more than one of these actions—magnesium stearate, for instance, is both an effective lubricant and an anti-adherent—which is

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why the single term “lubricant” is used loosely in practice [9].

Pharmaceutical lubricants are conventionally divided by their mechanism into boundary lubricants and fluid-film lubricants. Boundary lubricants, which include the metallic stearates and stearic acid, are solids that adhere to and coat the surfaces of granules and metal tooling, their long fatty-acid chains orienting to present a low-shear, low-friction interface; their effectiveness is governed by the surface area they cover and the strength of their adhesion to the substrate. Fluid lubricants, such as liquid paraffin and polyethylene glycols, act by interposing a fluid layer that separates the moving surfaces. The boundary stearates are by far the most widely used, and their behaviour dominates discussion of lubrication in solid-dosage manufacture.

The defining mechanistic feature of magnesium stearate, the most important pharmaceutical lubricant, is its laminar, plate-like crystal structure. During blending, the weakly bonded laminar sheets shear off the parent particles and smear over the surfaces of the granules and excipients, forming a thin hydrophobic film. This film simultaneously delivers the desired reduction in friction and, less desirably, coats the bonding sites between particles and repels water. The degree of coating is a direct function of the mechanical energy imparted during mixing—hence the central importance of lubrication time, which the later sections of this review address in detail [83, 88].

A useful way to appreciate the lubricant's outsized influence is to consider its quantity relative to its effect. Magnesium stearate is typically effective at 0.25 to 0.75% by weight in immediate-release tablets, yet at these minute concentrations it can reduce tablet tensile strength by a third or more and double the disintegration or mean dissolution time if blending is prolonged. This disproportion arises because the lubricant acts entirely at surfaces and interfaces rather than in bulk: a vanishingly thin film distributed over the enormous internal surface area of a powder bed is sufficient to transform both the frictional behaviour during compression and the wettability of the finished compact. It is for this reason that lubrication is treated as a distinct, carefully controlled unit operation rather than as ordinary blending, and why the lubricant is almost always added in a brief final step immediately before compression to limit the opportunity for over-coating [17, 21].

III. TYPES OF LUBRICANTS AND THEIR PROPERTIES

Lubricants may be classified by their solubility and surface character into hydrophobic and hydrophilic types, a distinction of direct consequence for drug release. The five lubricants considered in this review span this range and are summarised in Table 1; their relative hydrophobicity is depicted in Figure 2 and their multi-dimensional functional profiles in Figure 3.

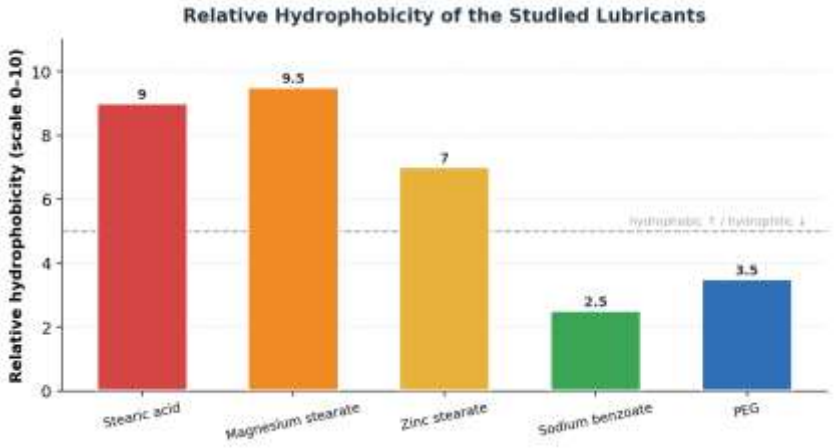

Figure 2. Relative hydrophobicity of the five studied lubricants. The metallic stearates and stearic acid are strongly hydrophobic, whereas sodium benzoate and polyethylene glycol are comparatively hydrophilic.

A. Hydrophobic Lubricants

Stearic acid is a long-chain saturated fatty acid widely used as a boundary lubricant. It forms a hydrophobic film around granules that reduces die-wall friction and improves compressibility, but the same film impedes water penetration and can therefore slow dissolution, particularly when used in excess; micronised grades offer good lubrication with a comparatively limited adverse effect on tensile strength [87]. Magnesium stearate is the single most widely used tablet lubricant, valued for its low coefficient of friction and large "covering potential," which deliver effective lubrication at very low concentrations—typically 0.25 to 0.75% for immediate-release tablets and up to about 5% in demanding applications. Its hydrophobicity is, however, the principal cause of the delayed disintegration, reduced hardness and slowed dissolution discussed throughout this review [82, 110]. Zinc stearate is a fatty-acid salt structurally analogous to magnesium stearate and used similarly to reduce friction; it is generally regarded as somewhat less hydrophobic, which may translate into a modestly smaller adverse effect on release, although it too retards dissolution if over-used.

B. Hydrophilic Lubricants

Sodium benzoate is a water-soluble lubricant whose action is milder than that of the stearates and which is far less prone to form a dense hydrophobic barrier. Because it does not greatly impede water penetration, it is favoured where faster drug release is desired, and its recognised antioxidant and antimicrobial preservative properties can additionally contribute to formulation stability. Polyethylene glycol (PEG) is a water-soluble polymer that functions as both a lubricant and a binder; its mild lubricating action is accompanied by a capacity to act as a plasticiser, improving tablet mechanical strength, and, being hydrophilic, it tends to support rather than hinder dissolution. The effect of PEG varies with molecular weight, lower-molecular-weight grades generally enhancing dissolution most. These hydrophilic materials illustrate the central trade-off of lubrication: they impose a smaller penalty on release but are, in general, less efficient friction-reducers than the stearates.

Table 1. Comparison of the five studied lubricants and their principal properties.

Lubricant	Hydrophobicity	Solubility	Effect on drug release
Stearic acid	High	Insoluble	Slows dissolution
Magnesium stearate	High	Insoluble	Slows dissolution (most pronounced)
Zinc stearate	Medium–high	Insoluble	Slows dissolution, less than Mg stearate
Sodium benzoate	Low	Water-soluble	Enhances / least hinders dissolution
Polyethylene glycol	Low–medium	Water-soluble	Enhances dissolution; aids compressibility

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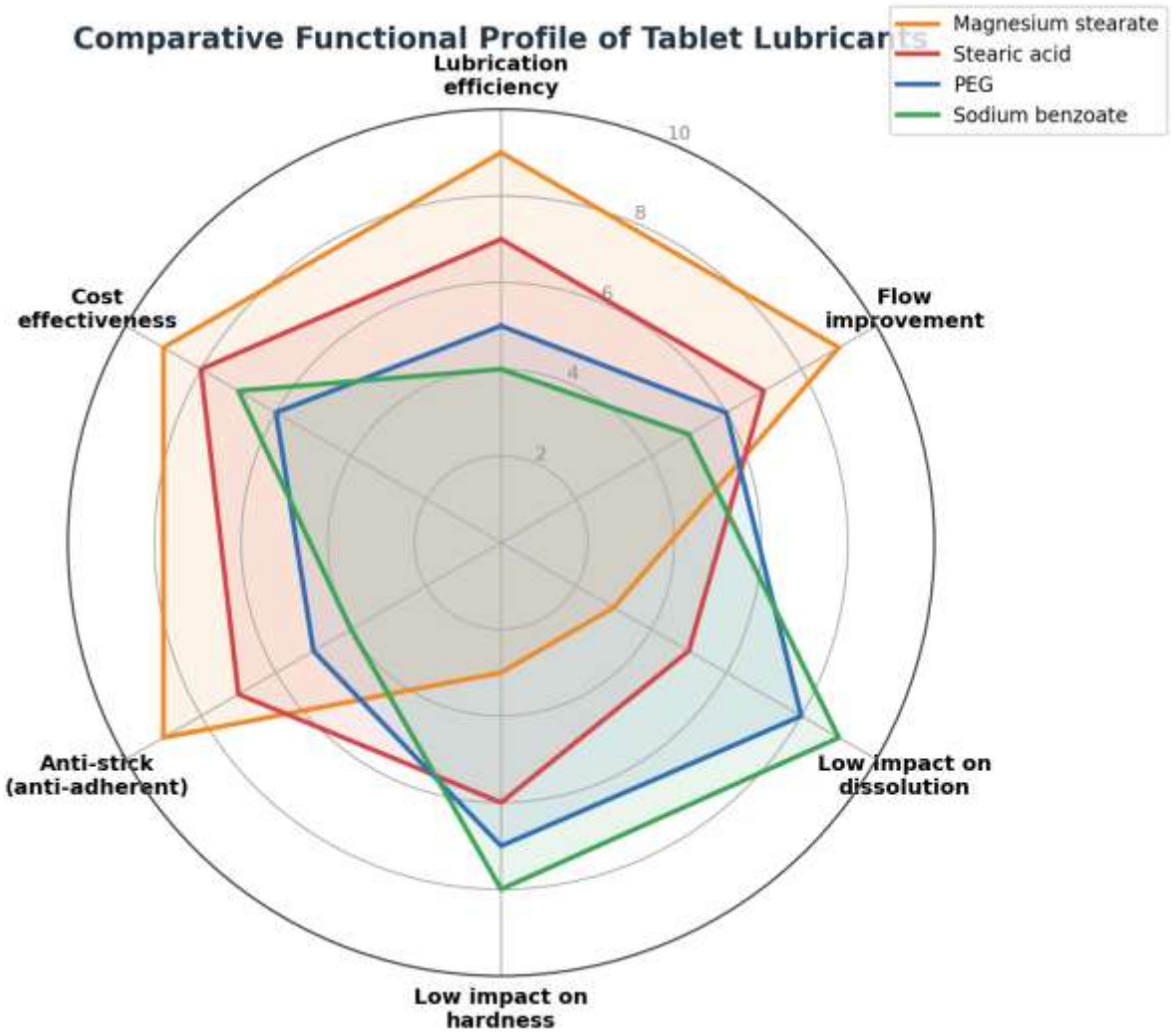

Figure 3. Comparative functional profile of representative lubricants across six performance attributes. Magnesium stearate excels at lubrication and flow improvement but scores poorly on its impact on dissolution and hardness; hydrophilic lubricants show the opposite balance.

IV. PARACETAMOL AS A MODEL DRUG AND THE GRANULATION PROCESS

Paracetamol (acetaminophen) is an almost universally used analgesic and antipyretic and a classic model drug for tablet-formulation studies, both because its dissolution characteristics are well understood and because its physical properties pose a recognised processing challenge. Paracetamol crystals exhibit notoriously poor flowability and poor compressibility, together with a marked tendency to cap and laminate under compression, owing to the prismatic shape of the crystals and their predominantly elastic deformation. As a direct consequence, paracetamol tablets are manufactured almost exclusively by wet granulation rather than direct compression, since granulation improves flow, compressibility and content uniformity [99, 102]. This makes paracetamol an apt and demanding system in which to study the effects of lubrication.

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Figure 4. The wet-granulation and tablet-compaction workflow used for a poorly compressible drug such as paracetamol, highlighting the lubrication step in which lubricant type and mixing time are varied.

In a representative wet-granulation process (Figure 4), the drug is first dry-blended with diluents such as microcrystalline cellulose and lactose monohydrate and with a disintegrant such as croscarmellose sodium. The blend is then granulated with an aqueous binder solution—commonly polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC)—in a high-shear granulator, and the wet mass is dried in a fluidised-bed dryer to a residual moisture of roughly two to three percent. The dried granules are sized by sieving, after which the lubricant is added and mixed for a defined lubrication time. The lubricated granules are finally compressed on a rotary tablet press to a defined weight and diameter under a controlled compression force [102]. It is the penultimate step—lubrication—that is the focus of this review, because the choice of lubricant and the duration of its blending exert a decisive influence on every downstream tablet attribute.

The roles of the principal excipient classes in this process are worth restating, since they interact with the lubricant. Diluents (fillers) such as microcrystalline cellulose and lactose provide bulk and influence compaction behaviour; importantly, plastically deforming materials such as microcrystalline cellulose are far more susceptible to the strength-reducing effect of lubricants than brittle, fragmenting materials such as lactose, because brittle fracture during compression continually exposes fresh, unlubricated surfaces at which interparticle bonds can form. Binders such as PVP and HPMC confer granule cohesion; disintegrants such as croscarmellose sodium promote tablet break-up and counteract the dissolution-retarding effect of hydrophobic lubricants; and the lubricant itself completes the blend [83, 90].

V. EFFECT OF LUBRICANT TYPE ON GRANULE AND TABLET PROPERTIES

A. Flowability

Adequate granule flow is a prerequisite for uniform die filling and hence for consistent tablet weight and content. Hydrophobic boundary lubricants, especially magnesium stearate, are highly effective glidants: their fine particles coat the host granules and fill surface asperities, reducing interparticulate friction and van der Waals attraction and so improving flow, frequently more effectively than hydrophilic additives. Magnesium stearate, for example, is reported to improve the flow of lactose at very low concentrations because its particles preferentially interact with and smooth the lactose surface [90, 97]. Flowability is most commonly quantified by the Carr's compressibility index and the Hausner ratio, both derived from the bulk and tapped densities of the granules, and these are discussed further in Section 8.

B. Compressibility and Tablet Hardness

Compressibility—the capacity of granules to deform and bond under pressure into a coherent compact—is reduced by lubrication, because the lubricant film interferes with the interparticle bonding on which tablet strength depends. The magnitude of this effect is strongly material-dependent: highly effective lubricants such as magnesium stearate produce the

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greatest reduction in tensile strength, and plastically deforming excipients such as microcrystalline cellulose are far more affected than brittle ones. Excessive lubrication therefore yields softer, weaker tablets, and the formulator must strike a balance between sufficient lubrication for manufacture and adequate hardness for handling and packaging [87, 90].

C. Disintegration and Drug Release

The most therapeutically significant consequence of lubricant choice is its effect on disintegration and dissolution. Hydrophobic lubricants form a water-repellent film that hinders the penetration of dissolution medium into the tablet, prolonging disintegration and slowing the release of the active; magnesium stearate is the most notorious in this respect, capable of measurably prolonging drug-liberation time and increasing disintegration time. Hydrophilic lubricants such as sodium benzoate and polyethylene glycol impose a far smaller penalty and may even facilitate faster disintegration and dissolution (Figure 1) [85, 87]. The incorporation of an efficient disintegrant can substantially offset the retarding effect of a hydrophobic lubricant, which is why such disintegrants are routine in immediate-release formulations.

VI. THE ROLE OF LUBRICATION TIME

If lubricant type sets the character of these effects, lubrication time—the duration for which the lubricant is blended with the granules—sets their magnitude. Lubrication differs fundamentally from ordinary blending: whereas most mixing aims at homogeneity, lubricant blending must distribute the lubricant sufficiently to function while avoiding the progressive over-coating of particle surfaces that degrades tablet quality. The optimal lubrication time is therefore a genuine optimum, not simply "as long as possible" [83, 88].

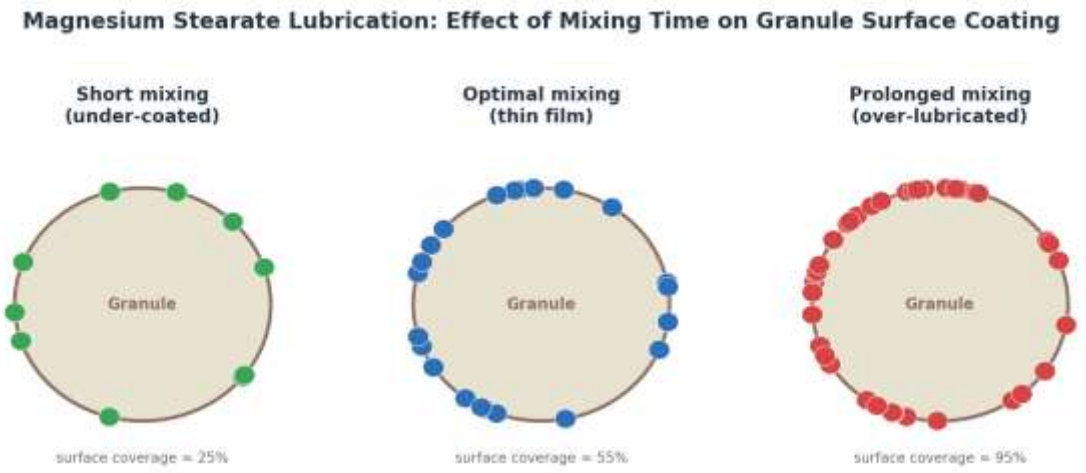

Figure 5. Effect of mixing time on the magnesium stearate film. Short mixing leaves granules under-coated; an optimal time gives a thin, functional film; prolonged mixing over-coats the surfaces, weakening interparticle bonding and repelling water ("over-lubrication").

A. Effect on Lubricant Distribution and Over-Lubrication

During blending, the laminar sheets of magnesium stearate progressively shear away and spread over the granule surfaces (Figure 5). For a short time this builds a beneficial, thin lubricating film. As mixing continues, however, the coating becomes more complete until the surfaces are extensively covered—a state known industrially as over-lubrication, or simply "the magnesium stearate effect." In the over-lubricated condition the lubricant film coats so much of the particle surface that it prohibits the interparticle bonding required for a strong compact and renders the granule surfaces strongly hydrophobic [83, 88]. Because even modest changes in mixing time, speed or mechanism alter the extent of this coating, lubrication time is one of the most sensitive and important process variables in tableting, and it is

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standard practice to add the lubricant in a brief, controlled final blending step and to sieve magnesium stearate beforehand to break up agglomerates.

B. Effect on Tablet Hardness, Disintegration and Release

The downstream consequences of prolonged lubrication are consistent and well documented (Figure 6). As lubrication time increases, tablet hardness falls because interparticle bonding is increasingly obstructed; disintegration time lengthens as the surfaces become more hydrophobic; and dissolution slows correspondingly. Classic studies by Kikuta and Kitamori, by Otsuka and colleagues and by Ragnarsson and co-workers established decades ago that extended mixing of magnesium stearate decreases tablet hardness and increases disintegration and dissolution times, and modern work has confirmed that the mean dissolution time of a blend can nearly double as mixing intensity rises [81, 83]. Conversely, shorter lubrication times yield a more porous, more readily wetted tablet and faster release—provided the time is not so short that the lubricant is poorly distributed, in which case granule flow and tablet uniformity suffer. The existence of opposing penalties at both extremes is precisely what makes lubrication time an optimisation problem.

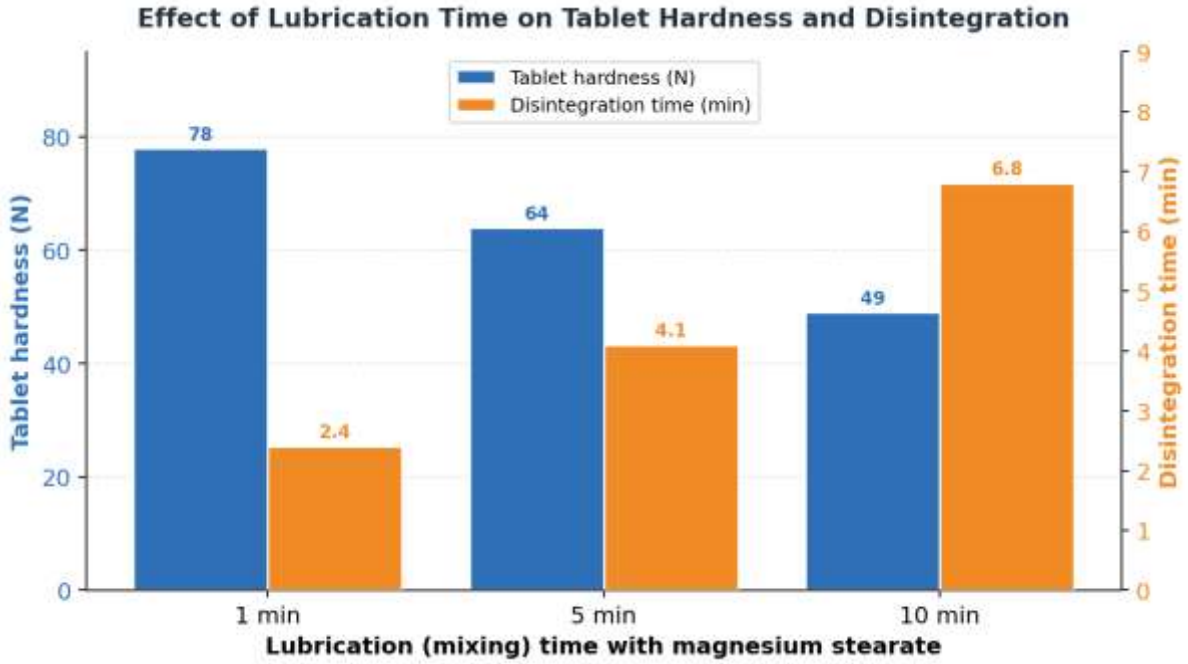

Figure 6. Illustrative effect of magnesium stearate lubrication time on tablet hardness and disintegration time. Prolonged mixing reduces hardness and lengthens disintegration, the signature of over-lubrication.

Figure 7 generalises this behaviour across lubricant types, showing that the hydrophobic stearates lose hardness most steeply with prolonged mixing, whereas the hydrophilic lubricants—being less prone to forming a continuous bonding-inhibiting film and more tolerant of over-mixing—are comparatively insensitive to lubrication time. This greater robustness to over-blending is one of the practical attractions of hydrophilic lubricants and of newer alternatives discussed in Section 10.

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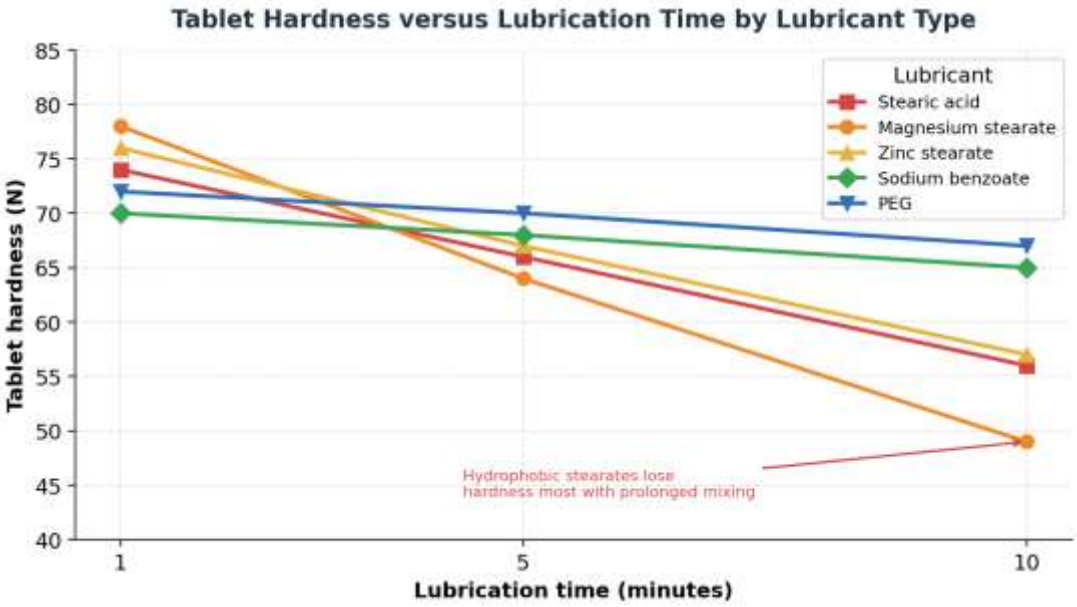

Figure 7. Tablet hardness versus lubrication time by lubricant type. Hydrophobic stearates show the steepest loss of hardness with prolonged mixing; hydrophilic lubricants are far more tolerant of over-blending.

VII. FACTORS INFLUENCING THE LUBRICATION OUTCOME

The effect of a lubricant on a given tablet formulation is not fixed but emerges from the interaction of several variables, of which lubricant type and lubrication time are the two examined most closely in this review. A clear appreciation of the full set of factors is essential to rational formulation, because changing any one of them can shift the balance between adequate manufacture and acceptable drug release. The principal variables and their typical influence are summarised in Table 2.

Table 2. Principal factors governing the effect of lubrication on tablet quality.

Factor	Typical influence on tablet quality
Lubricant type / hydrophobicity	Hydrophobic stearates retard release; hydrophilic lubricants have far less effect
Lubricant concentration	Higher levels improve lubrication but reduce hardness and slow dissolution
Lubrication (mixing) time	Longer time over-coats granules: lower hardness, longer disintegration
Mixing intensity / shear	Greater shear accelerates film formation and over-lubrication
Excipient deformation type	Plastic materials (e.g. MCC) more affected than brittle ones (e.g. lactose)
Disintegrant presence	Offsets the dissolution-retarding effect of hydrophobic lubricants

Two of these factors deserve particular emphasis alongside lubrication time. First, lubricant concentration acts in the same direction as mixing time: increasing the amount of a hydrophobic lubricant, like increasing the duration of its blending, improves lubrication efficiency while progressively reducing tablet hardness and slowing disintegration and dissolution, so that concentration and time must be considered together. Second, the deformation behaviour of the bulk excipients modulates the entire response. Plastically deforming materials such as microcrystalline cellulose retain the lubricant film at their bonding interfaces and so suffer the greatest loss of strength, whereas brittle, fragmenting materials such as lactose continually generate fresh, unlubricated surfaces during compression at which bonding can still occur, rendering them far more tolerant of lubrication. The choice of filler therefore

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conditions how sensitive a formulation will be to both lubricant type and lubrication time [21, 30].

A. Internal versus External Lubrication

A further variable is the manner in which the lubricant is introduced. In conventional internal lubrication the lubricant is blended into the granules before compression, which inevitably coats the particle surfaces and produces the strength- and dissolution-reducing effects described above. In external lubrication, by contrast, the lubricant is applied directly to the surfaces of the punches and die—often as a fine spray or dust—so that it performs its friction-reducing role at the tooling interface without being incorporated into the tablet matrix. External lubrication can therefore deliver adequate lubrication while largely preserving tablet tensile strength and release, and it has been investigated as a means of mitigating the detrimental effects of internal magnesium stearate, particularly for mini-tablets and high-speed presses, although it requires specialised equipment and careful control to ensure uniform application [3, 11].

VIII. ANALYTICAL EVALUATION PARAMETERS

Validating the effects of lubricant type and lubrication time requires a defined battery of analytical tests spanning granule flow, tablet mechanical strength and drug release.

A. Granule Flowability

Flow is assessed from the bulk and tapped densities of the granules through two derived indices. The Carr's compressibility index, calculated as the percentage difference between tapped and bulk density, classifies flow from excellent (≤10%) through good, fair and passable to poor and very poor at progressively higher values (Figure 8); a Carr's index below about 15% indicates good flowability. The Hausner ratio, the ratio of tapped to bulk density, conveys the same information, with values below about 1.25 denoting good flow and values above roughly 1.35 to 1.4 indicating poor flow. Both are codified in the United States Pharmacopeia general chapter on powder flow and are complemented by the angle of repose and, for more rigorous work, shear-cell flow-function measurements [91, 92, 95].

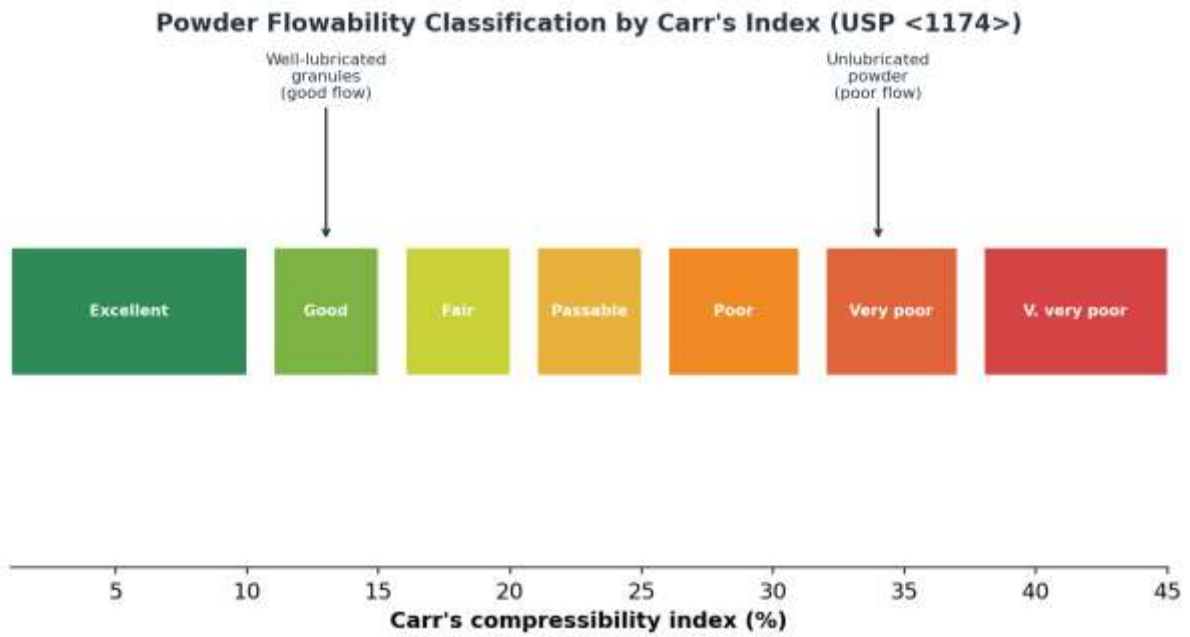

Figure 8. Powder flowability classification by Carr's compressibility index (USP <1174>). Effective lubrication typically moves granules into the good-to-excellent flow range, whereas unlubricated powder often falls in the poor-flow region.

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B. Tablet Hardness and Disintegration

Tablet hardness (crushing strength), the force required to fracture a tablet, is measured with a hardness tester and reported in newtons; it indexes the mechanical strength needed to survive handling, packaging and transport, and, as discussed, it is reduced both by hydrophobic lubricants and by prolonged lubrication time. Disintegration time, the time for a tablet to break apart completely in a specified medium, is determined in a pharmacopoeial disintegration apparatus and is a key early indicator of how rapidly the drug will become available; it is lengthened by hydrophobic lubricants and by over-lubrication.

C. Dissolution Testing and Release Kinetics

Dissolution testing measures the rate and extent of drug release into a defined medium and is the most direct biopharmaceutical assessment of lubricant effects. For a paracetamol formulation, dissolution is typically performed in a USP apparatus in 900 mL of 0.1 N hydrochloric acid at 37 °C with defined agitation, with samples withdrawn at intervals and assayed for paracetamol by ultraviolet spectrophotometry at 243 nm (Figure 9) [98]. The resulting release data are commonly fitted to kinetic models—zero-order, first-order, the Higuchi diffusion model and the Korsmeyer–Peppas power-law model—to elucidate the release mechanism, with the Korsmeyer–Peppas release exponent distinguishing diffusion-controlled (Fickian) release from erosion-controlled and anomalous transport. Such modelling provides a rigorous, comparative description of how lubricant type and lubrication time reshape the release profile.

Comparing the fitted models across formulations sharpens the interpretation of lubricant effects. A hydrophobic, over-lubricated tablet that resists wetting tends to release its drug more slowly and more diffusion-dependently, so that its profile is well described by the Higuchi or Korsmeyer–Peppas model with a release exponent indicative of Fickian diffusion through a poorly penetrated matrix. A rapidly disintegrating, hydrophilically lubricated tablet, by contrast, releases its drug promptly upon disintegration, and its early profile is dominated by dissolution rather than by slow diffusion. Reporting the best-fit model together with its rate constant and correlation coefficient therefore allows the influence of lubricant type and lubrication time to be expressed not merely as a change in the percentage released at a fixed time, but as a change in the underlying release mechanism—information of considerable value when troubleshooting a formulation or defending it to a regulator.

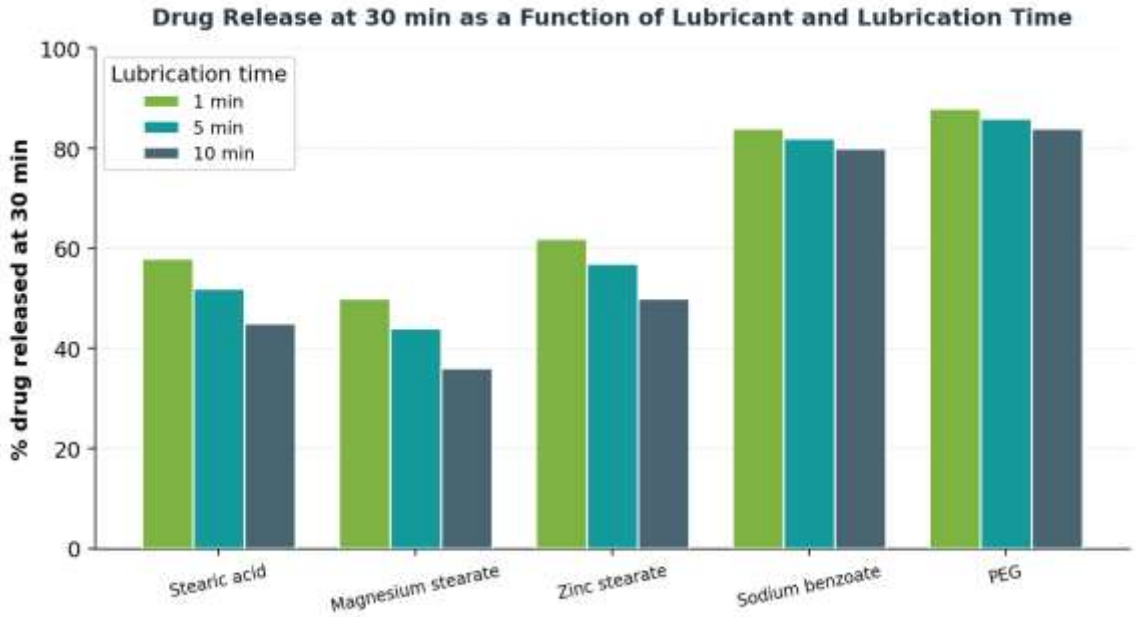

Figure 9. Illustrative drug release at 30 minutes as a function of lubricant type and lubrication time. Release falls with increasing lubrication time for every lubricant, the decline being steepest for the hydrophobic stearates.

D. Scanning Electron Microscopy

Scanning electron microscopy (SEM) provides direct, qualitative confirmation of the mechanisms inferred from the quantitative tests. By imaging the surfaces of granules and tablets at high magnification, SEM reveals the extent and uniformity of lubricant coating, allowing the under-coated, optimally coated and over-coated states to be visualised and correlated with the measured hardness, disintegration and dissolution. SEM thus complements the bulk measurements with mechanistic, surface-level evidence of the effects of lubrication time.

IX. EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS

Because lubricant type and lubrication time are two independent factors each acting at several levels, their study lends itself to a structured experimental design. A common approach is a completely randomised design in which the lubricant type (the five materials considered here) and the lubrication time (for example one, five and ten minutes) are varied systematically and each formulation is prepared and tested in replicate to ensure reproducibility. The measured responses—Carr's index and Hausner ratio for flow, hardness in newtons, disintegration time in minutes and percentage drug released at defined intervals—capture the full chain from granule property to drug release.

The resulting data are analysed by analysis of variance (ANOVA) to determine whether lubricant type, lubrication time and their interaction exert statistically significant effects on each response, with post-hoc multiple-comparison procedures such as Tukey's honestly significant difference test used to identify which specific formulations differ, conventionally at a significance threshold of $p < 0.05$. More elaborate studies employ formal design-of-experiments methodologies, including factorial and response-surface designs, to model the responses as functions of the factors and to locate the optimum combination of lubricant and lubrication time. This statistical framework converts what might otherwise be a series of isolated observations into a quantitative, predictive understanding of how the two variables jointly govern tablet performance, and it embodies the Quality-by-Design philosophy increasingly expected by regulators [82].

The practical objective of such a study is to identify, for each lubricant, the lubrication time that achieves the best compromise between competing requirements. Too little lubrication compromises granule flow, die filling and weight uniformity and risks sticking and high ejection forces; too much compromises tablet strength and slows disintegration and dissolution. The optimum for a strongly hydrophobic lubricant such as magnesium stearate is therefore typically a short, tightly controlled mixing time, whereas a more hydrophilic and over-mixing-tolerant lubricant offers a wider operating window within which acceptable tablets can be produced. Expressed in the language of the present study's design, the interaction term between lubricant type and lubrication time is expected to be statistically significant, because the penalty for prolonged mixing is far greater for the hydrophobic stearates than for the hydrophilic lubricants—precisely the pattern illustrated in Figures 6, 7 and 9. Establishing this interaction quantitatively is the central scientific contribution that a well-designed lubrication study can make.

X. ALTERNATIVE LUBRICANTS, MARKET CONTEXT AND FUTURE PERSPECTIVES

The well-known limitations of magnesium stearate have driven interest in alternative lubricants that retain its efficiency while reducing its adverse effects. Sodium stearyl fumarate, a more hydrophilic lubricant effective at low concentrations (typically 0.25 to 3%), is the most prominent: it has a smaller negative impact on disintegration and dissolution, greater tolerance of over-mixing and better compatibility with sensitive actives, and has been reported to cut disintegration time relative to magnesium stearate in moisture-sensitive modified-release tablets, albeit at higher cost [108, 112]. Micronised stearic acid grades, calcium stearate, glyceryl behenate, talc and sodium lauryl sulfate provide further options, each occupying a particular niche defined by the trade-off between lubrication efficiency and the impact on tablet quality [116].

The commercial scale of this field is considerable. Magnesium stearate remains the dominant tablet lubricant—its dedicated market valued at several hundred million US dollars and growing steadily—while the broader stearate and pharmaceutical-excipient markets are larger still, with India's excipient market alone projected to reach around US$1.2 billion, reflecting the expansion of generic and nutraceutical manufacture in the Asia-Pacific region [107, 114]. Sustainability pressures are reshaping supply, with a marked shift toward vegetable-derived, palm-free and "clean-label" excipient grades.

Looking forward, several trends are likely to refine lubrication practice. External lubrication, in which the lubricant is applied directly to the punches and die rather than blended into the granules, offers a means of obtaining adequate lubrication while largely avoiding the strength- and dissolution-reducing effects of internal lubrication, and is being systematically evaluated for mini-tablets and high-speed presses. The shift toward continuous manufacturing places a premium on understanding and controlling the shear history—and hence the effective lubrication time—experienced by the blend, motivating predictive, model-based approaches to lubrication. And the wider adoption of process analytical technology and design-of-experiments methodology is enabling the lubrication step to be characterised and optimised with far greater rigour than the empirical practice of the past. Each of these developments serves the same end identified throughout this review: achieving sufficient lubrication for efficient, robust manufacture without compromising the mechanical strength and drug-release performance of the finished tablet.

XI. CONCLUSION

Lubricants are small in quantity but decisive in effect, and their influence on the compaction and drug-release behaviour of granules is governed jointly by their chemical nature and by the lubrication time over which they are blended. Hydrophobic boundary lubricants—magnesium stearate foremost among them, with stearic acid and zinc stearate close behind—are highly efficient friction-reducers and flow improvers, but their laminar films coat granule surfaces, inhibit interparticle bonding and repel water, thereby reducing tablet hardness and prolonging disintegration and dissolution. The more hydrophilic sodium benzoate and polyethylene glycol impose a far smaller penalty on release and are more tolerant of processing, at the cost of somewhat lower lubrication efficiency. Superimposed on the choice of lubricant, lubrication time sets the magnitude of these effects: too short a time leaves the lubricant poorly distributed and flow and uniformity suffer, while too long a time over-coats the granules—the classic over-lubrication or "magnesium stearate effect"—softening the tablet and slowing release. Using paracetamol, a poorly compressible model drug manufactured by wet granulation, as the reference system, this review has shown that lubricant selection and lubrication time constitute a coupled optimisation problem, best resolved through a statistically designed, Quality-by-Design approach supported by a full battery of flow, mechanical and dissolution testing. A judicious balance—an adequately efficient lubricant blended for an optimal, controlled time, with disintegrant support where rapid release is required—yields tablets that are at once manufacturable, mechanically robust and therapeutically effective.

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