

UNIVERSITÉ FERHAT ABBAS SÉTIF 1
FACULTÉ DE MÉDECINE



DÉPARTEMENT DE PHARMACIE

Mémoire De Fin D'étude En Vue De L'obtention
Du Diplôme De Docteur En Pharmacie

Thème

**OPTIMIZATION OF CO-PROCESSED EXCIPIENTS FOR DIRECT
COMPRESSION OF HIGH-DOSE APIS: COMPARATIVE STUDY
AND FORMULATION DEVELOPMENT**

Soutenue publiquement le : 01/07/2026

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Année Universitaire 2025/2026

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ABSTRACT

Direct compression (DC) remains the most cost-effective and streamlined manufacturing route in solid dosage formulation, yet its application is often limited by the poor mechanical properties of high-dose active pharmaceutical ingredients (APIs). This study investigated the optimization and maximum carrying capacity of the co-processed excipient Prosolv (Silicified Microcrystalline Cellulose) for the direct compression of a high-dose, highly cohesive API with poor flowability and compressibility: Paracetamol (500 mg). The core objective was to bypass traditional granulation steps entirely. Formulations were developed using varying percentages of Prosolv, lubricated with 0.5% magnesium stearate, and subjected to a range of compression forces. The formulations yielded defect-free tablets with satisfactory size and robust compressibility profile; however, this success was exclusively achieved at high excipient concentrations of 50% and 60% Prosolv. These findings challenge the initial hypothesis that standard co-processed excipients can readily accommodate high-dose formulations at low percentages to maintain standard tablet weights. While Prosolv successfully mitigated the poor compaction properties of Paracetamol, the required high excipient load limits its practicality for high-dose APIs due to the resulting large tablet size, and the cost of manufacturing the tablets at a large scale with this particular formulation. Consequently, further studies are required to explore alternative co-processed excipient composites or altered component ratios to optimize direct compression for high-dose formulations.

Keywords: **Direct Compression, Co-processed Excipients, High-dose APIs, Paracetamol, Microcrystalline Cellulose (MCC), Compactibility, Dilution Capacity, Solid Dosage Form.**

ABSTRACT

La compression directe (CD) demeure la voie de fabrication la plus économique et la plus rationalisée en formulation galénique solide. Néanmoins, son application est souvent limitée par les faibles propriétés mécaniques des principes actifs (PA) fortement dosés. Cette étude a évalué l'optimisation et la capacité de charge maximale de l'excipient co-transformé Prosolv (cellulose microcristalline silicifiée) pour la compression directe d'un PA fortement dosé et hautement cohésif, présentant une coulabilité et une compressibilité médiocres : le paracétamol (500 mg). L'objectif principal était de s'affranchir totalement des étapes de granulation traditionnelle. Des formulations ont été développées en faisant varier les pourcentages de Prosolv, lubrifiées avec 0,5 % de stéarate de magnésium, puis soumises à différentes forces de compression. Ces formules ont permis d'obtenir des comprimés exempts de défauts, de taille satisfaisante et dotés d'un profil de compressibilité robuste ; toutefois, ce succès a été exclusivement atteint avec des concentrations d'excipient élevées, à savoir 50 % et 60 % de Prosolv. Ces résultats remettent en question l'hypothèse initiale selon laquelle les excipients co-transformés standards peuvent facilement intégrer des formulations fortement dosées à de faibles pourcentages afin de maintenir un poids de comprimé standard. Bien que le Prosolv ait réussi à pallier les faibles propriétés de compaction du paracétamol, la forte charge d'excipient requise limite son intérêt pratique pour les PA fortement dosés, en raison de la taille importante du comprimé qui en découle et du coût de fabrication à grande échelle avec cette formulation spécifique. Par conséquent, d'autres études sont nécessaires pour explorer de nouveaux composites d'excipients co-transformés ou modifier les proportions des composants afin d'optimiser le compactage direct des formulations fortement dosées.

Mots clefs : Compression Directe, Excipients co-traités, Principes actifs à forte dose, Paracétamol, Cellulose microcristalline, Compactibilité, Capacité de dilution, Formes galéniques solides.

الملخص

لا يزال الضغط المباشر المسار التصنيعي الأكثر اقتصادية وانسيابية في إنتاج الأشكال الصيدلانية الصلبة ومع ذلك، فإن تطبيقه غالباً ما يواجه تحديات ناجمة عن ضعف الخواص الميكانيكية للمواد الفعالة ذات الجرعات العالية

هدفت هذه الدراسة إلى تقييم الكفاءة والقدرة الاستيعابية القصوى للسواغ المدمج «بروسولف» (السليولوز دقيق التبلور السيليكوني) في تحضير أقراص بالضغط المباشر لمادة الباراسيتامول بجرعة 500 ملغ، وهي مادة فعالة معروفة بشدة تماسكها، وضعف انسيابيتها، وانخفاض قابليتها للانضغاط. كما سعت الدراسة إلى الاستغناء الكامل عن مراحل التحبيب التقليدية.

تم تحضير عدة صيغ صيدلانية بنسب مختلفة من «بروسولف»، مع إضافة 0.5% من ستيرات المغنيسيوم كمادة مزلفة، ثم خضعت الخلطات لقوى كبس متفاوتة. وأظهرت النتائج إمكانية إنتاج أقراص خالية من العيوب التصنيعية، ذات حجم مقبول ومنحنى انضغاطية جيد، إلا أن هذا النجاح تحقق فقط عند استخدام نسب مرتفعة من السواغ بلغت 50% و 60%.

تشير هذه النتائج إلى أن السواغات المدمجة القياسية قد لا تكون قادرة على استيعاب المواد الفعالة عالية الجرعة عند نسب منخفضة، وهو ما يتعارض مع الفرضية الأساسية للدراسة. فعلى الرغم من نجاح «بروسولف» في تحسين قابلية انضغاط الباراسيتامول، فإن الحاجة إلى استخدامه بكميات كبيرة تحد من جدواه العملية، بسبب زيادة حجم القرص وارتفاع تكلفة الإنتاج على المستوى الصناعي

وبناءً على ذلك، توصي الدراسة بإجراء المزيد من الأبحاث لتطوير سواغات مدمجة بديلة، أو تحسين نسب مكوناتها، بما يحقق أعلى كفاءة ممكنة لعمليات الضغط المباشر في المستحضرات الدوائية ذات الجرعات العالية

الكلمات المفتاحية: السواغات المدمجة، المواد الفعالة عالية الجرعة، الباراسيتامول، السليولوز دقيق التبلور السيليكوني، (بروسولف)، القابلية للانضغاط، القدرة الاستيعابية، الأشكال الصيدلانية الصلبة.