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# Multiparticulate System of Diacerein Loaded Eudragit Beads: Enhancing Yield and Efficiency through Modified Sieving/Spheronization Technique

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**Abstract**

This study investigates the formulation of multiparticulate systems aimed at improving the delivery of diacerein, a potent agent in osteoarthritis (OA) treatment, utilizing Eudragit beads via extrusion spheronization. The study addresses key challenges associated with diacerein through systematic polymer selection, formulation optimization, and comprehensive characterization, including its poor solubility, variable absorption, and gastrointestinal side effects. By employing innovative sieving/spheronization techniques, the study achieves significant reductions in material wastage, enhances formulation yield, and ensures the production of uniform, spherical pellets with superior drug release properties. Optimization strategies facilitated by DesignExpert® software lead to the identification of formulation parameters conducive to achieving desired drug release kinetics and mechanical characteristics. The successful scaling up of the optimized batch confirms the effectiveness of the approach, underlining the potential of multiparticulate systems as a promising avenue for optimizing diacerein delivery in OA therapy. Further investigations may focus on refining formulations and conducting preclinical efficacy evaluations to fully elucidate the therapeutic benefits of multiparticulate systems in OA management.

Keywords

Multiparticulate systems, Extrusion, Spheronization, Osteoarthritis, Eudragit beads

## 1 Introduction

Osteoarthritis (OA) is a prevalent chronic degenerative joint disease characterized by progressive cartilage degradation, synovial inflammation, and alterations in the subchondral bone (He et al., 2020). It is a leading cause of disability worldwide, affecting millions of individuals across diverse demographics (Steinmetz et al., 2023). The management of OA poses significant challenges to healthcare providers due to the complex interplay of genetic, environmental, and biomechanical factors contributing to its pathogenesis (Liu et al., 2023). Despite the array of treatment options available, ranging from analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) to surgical interventions such as joint replacement, the current therapeutic armamentarium remains suboptimal in terms of efficacy, safety, and long-term outcomes (Ackerman et al., 2019; Costa et al., 2021; Young et al., 2023).

The quest for more effective and safer therapeutic modalities has fueled research into innovative drug delivery systems tailored for OA treatment. Multiparticulate drug delivery systems have garnered considerable interest recently due to their potential to enhance drug bioavailability, optimize pharmacokinetics, and improve patient compliance (Komati et al., 2019). Unlike conventional dosage forms, which often suffer from dose dumping and erratic absorption, multiparticulate systems offer several advantages, including uniform drug distribution, reduced risk of local irritation, and the ability to tailor release kinetics to match the desired therapeutic profile (Priese et al., 2023).

In this context, using Eudragit, a family of biocompatible and pH-sensitive polymers, holds promise for developing multiparticulate formulations targeting OA (dos Santos et al., 2021). Eudragit polymers exhibit pH-dependent solubility characteristics, allowing for selective drug release in response to changes in the physiological environment (Nikam et al., 2023). This property is particularly advantageous for OA therapy, where localized drug delivery to the inflamed joint is desired to maximize therapeutic efficacy while minimizing systemic exposure and adverse effects.

Diacerein (DIN), a potent anthraquinone derivative, has emerged as a promising pharmacological agent for OA management (Pavelka et al., 2016). Its multifaceted mechanism of action includes inhibition of interleukin-1β (IL-1β) synthesis (Silva et al., 2022), suppression of matrix metalloproteinases (MMPs) (Sirikaew et al., 2019), and stimulation of glycosaminoglycan synthesis (Kongtharvonskul et al., 2016), thereby exerting chondroprotective, anti-inflammatory, and analgesic effects (Timur et al., 2020). However, diacerein's poor aqueous solubility and limited systemic bioavailability hinder its clinical utility (Fouad et al., 2021), resulting in variable therapeutic outcomes and gastrointestinal intolerance, including diarrhoea and abdominal discomfort (Zeng et al., 2023).

The rationale behind this study lies in the imperative to address the unmet clinical needs in OA management by developing a multiparticulate system of diacerein-loaded Eudragit beads. The drug has a short half-life, mandating frequent dosing. It is reported to have variable and incomplete oral absorption, leading to diarrhoea and urine of yellow-brown colouration. It also has a poor oral bioavailability of 35-56 %, which could be attributed to its low aqueous solubility of 3.197 mg/L (El-Laithy et al., 2015).

Considerable efforts have been documented in the scientific literature to address the challenges associated with DIN. For instance, conventional melting techniques have been employed to formulate surfactant-based solid dispersions of DIN (Patil et al., 2010). Furthermore, inclusion

complexes of DIN have been synthesized utilizing β-cyclodextrin and hydroxypropyl β-cyclodextrin via the kneading method (Batt & Garala, 2013). DIN-loaded solid lipid nanoparticles have been developed to enhance drug delivery using a modified high-shear homogenization and ultra-sonication approach (Jain et al., 2013). Additionally, niosomes and mixed niosomes have been utilized to encapsulate DIN as a model for poorly water-soluble drug molecules, employing various surfactant/cholesterol ratios (El-Say et al., 2016). Furthermore, DIN nanosuspensions have been fabricated through sonoprecipitation, followed by chitosan coating, within the same context of enhancing drug solubility and bioavailability (Allam et al., 2017).

Innovative formulation strategies are warranted to overcome these challenges and harness the therapeutic potential of diacerein. Among these, the development of multiparticulate systems offers a promising avenue for enhancing diacerein's solubility, stability, and efficacy in OA therapy. Encapsulating diacerein within Eudragit beads envisages that the multiparticulate system can facilitate sustained drug release, improve drug solubility, and enhance therapeutic efficacy, thereby overcoming the inherent limitations of diacerein administration, including poor solubility, variable absorption, and gastrointestinal side effects.

Extrusion spheronization, a widely employed pharmaceutical technique, provides a robust and scalable method for preparing spherical multiparticulate systems. Combining extrusion and spheronization processes can produce uniform spherical beads with controlled size and drug loading characteristics, ensuring reproducibility and consistency in formulation. This technique offers versatility in selecting excipients and process parameters, allowing for optimization of drug release kinetics and biopharmaceutical properties.

Furthermore, extrusion spheronization facilitates the production of spherical beads with precise control over size, shape, and drug loading, ensuring reproducibility and scalability of the formulation process (Muley et al., 2016). Through systematic characterization and evaluation, including in vitro dissolution studies, pharmacokinetic profiling, and preclinical efficacy assessments, this study aims to elucidate the potential of the multiparticulate system in enhancing the therapeutic outcomes of diacerein for OA treatment.

Thus, developing a multiparticulate system comprising diacerein-loaded Eudragit beads via extrusion spheronization represents a promising approach for managing OA. By addressing the challenges associated with diacerein administration, this innovative formulation strategy holds the potential to revolutionize the current landscape of OA therapy, offering improved efficacy, safety, and patient compliance.

## 2 Materials and methods

For experimental purposes, Diacerein (DIN), an anthraquinone derivative, was acquired as a complimentary sample from IPCA Pharmaceuticals, Mumbai, India. Various excipients essential for formulation development were obtained, including Eudragit polymers (S-100, E-100, and RS-100), generously provided by Evonik Industries, India. Additionally, ethyl cellulose, microcrystalline cellulose, and polyvinylpyrrolidone K-30 (PVP K-30) were procured from Research Lab Fine Chem Industries, India. Furthermore, sodium lauryl sulphate and sodium hydroxide were sourced from the same supplier. Solvents such as dimethyl sulfoxide (DMSO), methanol, ethanol, dichloromethane, acetone, and hydrochloric acid were purchased from S.D. Fine Chemicals, Mumbai, India. Notably, all chemicals utilized in the

formulation were of analytical grade, ensuring their purity and suitability for pharmaceutical applications.

**2.1 Preparation of DIN-loaded pellets**

2.1.1 Selection of the polymer

The selection of polymers for the formulation of sustained-release pellets of diacerein (DIN) involved a systematic screening process. Hydroxypropyl methylcellulose (HPMC) K4M, ethyl cellulose (EC), and Eudragit S-100 (S-100), as well as various combinations thereof, were evaluated. The objective was to identify polymer combinations that would yield pellets with desirable organoleptic properties and achieve controlled in vitro drug release profiles (Kaur et al., 2020; Maboos et al., 2018; Mallipeddi et al., 2014).

2.1.2 Selection of the concentration of the wetting agent

The concentration of sodium lauryl sulfate (SLS) was systematically varied throughout the pellet preparation process to investigate its influence on in vitro drug release kinetics. Different concentrations of SLS were incorporated into the pellet formulations, and the resultant pellets were subjected to in vitro dissolution testing to assess their drug release profiles.

2.1.3 Modified sieving/spheronization technique

The extrusion/spheronization technique was employed for pellet preparation. Accurate weighing of the drug and other constituents was performed, followed by thorough mixing to create a dough utilizing water as the solvent. Subsequently, extrudes were formed using an extruder, and these extrudates were then placed onto the plate of the spheronizer, with the spheronizer speed set to 1000 rpm. After 2-3 minutes, the pellets were harvested and subjected to air drying, followed by tray drying below 50 °C for 20 minutes to ensure complete removal of the granulating fluid.

Significant material wastage occurred during the extrusion/spheronization process due to the material's adherence to the extruder. To mitigate such issues and optimize formulation yield, a slight modification was introduced solely in the extrusion step. The method was hence modified to sieving/spheronization. All ingredients were accurately weighed, and the dough was formed using water as the granulating liquid. The dough was then sieved to generate extrudates, which were subsequently subjected to spheronization at 1000 rpm for 2-3 minutes to yield spherical pellets.

This modified sieving and spheronization approach allowed for the preparation of a batch size ranging from 4 to 5 grams, thereby reducing excess material usage and consequent losses. Sieves of various sizes ranging from 8# to 36# were tried to give pellets with the desired size and highest yield. Notably, this method exhibited a yield of 95%, in contrast to the 50% yield observed with conventional extrusion. Subsequently, the percentage cumulative drug release from the prepared formulation was assessed. The final process used in the formulation of pellets is depicted in Figure 1.

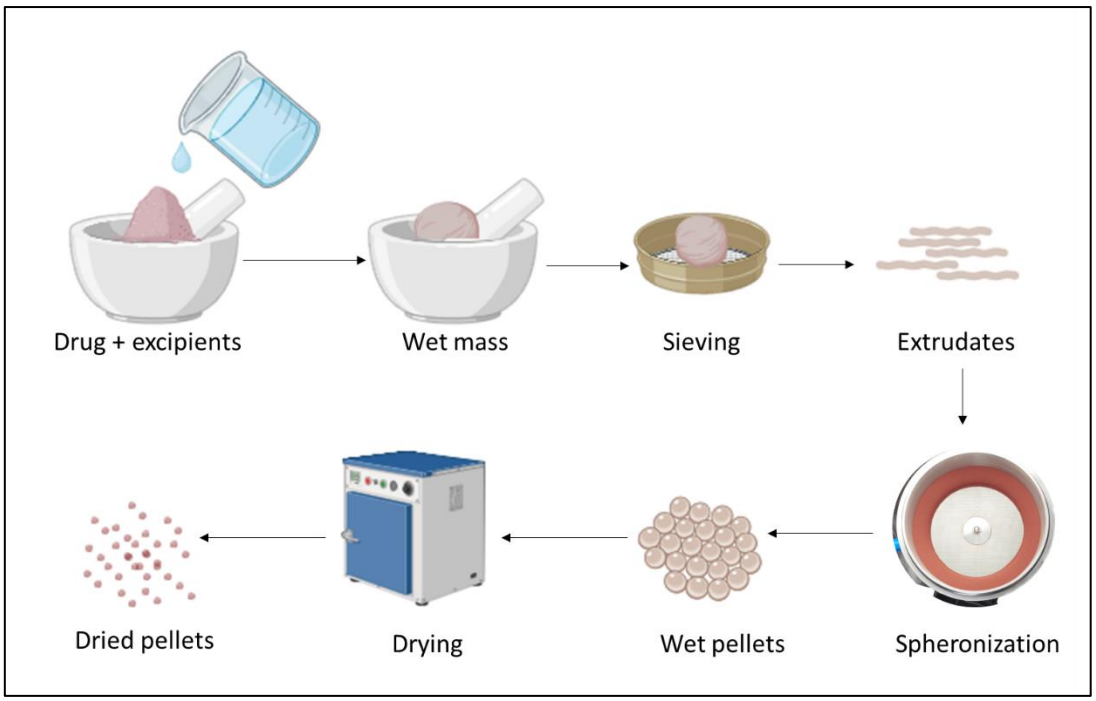


Figure 1: Steps in the fabrication of DIN-loaded pellets (Created with BioRender.com)

2.2 Optimization of pellet formulation

The formulation was optimized employing a $3^2$-factorial design. The independent variables identified from earlier experimentation were the polymer and binder concentrations. The impact of these variables was studied using ANOVA on pellet strength and in vitro drug release. StatEase Design Expert software was used to construct the study design and analyze the data. The batch showing the best organoleptic characteristics with the highest drug release was scaled up for further evaluation. The procedure to assess the strength of the pellet and the in vitro drug release was given hereunder.

2.2.1 Crushing strength of the pellets

The strength of the pellets was assessed using a digital hardness meter (Dolphin, India). The results were expressed in Kg (Hiew et al., 2020).

2.2.2 In vitro drug release

The pellets' in vitro drug release profile was evaluated employing a USP dissolution apparatus type I, operating at 75 rpm. A phosphate buffer solution with a pH of 7.4, totalling 900 mL, served as the dissolution medium. Pellets equivalent to a single dose were utilized for the investigation. At hourly intervals over 12 hours, aliquots were withdrawn from the dissolution medium. These samples were subsequently filtered and suitably diluted, and their absorbance was measured using a UV-Vis spectrophotometer set to a wavelength of 257 nm.

2.3 Evaluation of pellets

2.3.1 Morphological characterization

Pellets were placed onto glass slides and covered with coverslips to evaluate pellet shape and size. The Motic microscope was then adjusted to the desired magnification settings. Pellets were systematically observed, focusing on size, shape, and surface characteristics. Representative images were captured using the Motic ImagePlus 2.0 software (Pande et al., 2019).

2.3.2 Assay

To assess entrapment efficiency, pellets were meticulously triturated and suspended in a minimal quantity of dimethyl sulfoxide (DMSO). Subsequently, the suspension underwent appropriate dilution with distilled water before being filtrated to isolate shell fragments. Drug estimation was performed utilizing a UV-Vis spectrophotometer set at a wavelength of 257 nm. The experiments were performed in triplicate, and the results are expressed as mean ± standard deviation.

2.3.3 In vitro drug release profile and kinetics

The in vitro drug release of the pellets for 12 hours was studied using the procedure described earlier. The kinetics of drug release were determined using the curve-fitting approach (Bruschi, 2015).

**3 Results and discussion**

3.1 Preparation of DIN-loaded pellets

3.1.1 Selection of the polymer

Hydroxypropyl methylcellulose (HPMC) K4M, ethyl cellulose (EC), and Eudragit S-100 (S-100) were chosen for evaluation due to their well-established track record in pharmaceutical formulations as sustained-release agents. Each polymer offers distinct characteristics that can influence drug release kinetics and pellet properties. HPMC K4M is known for its excellent film-forming properties and ability to modulate drug release through hydration and swelling mechanisms (Pan et al., 2023). Ethylcellulose, being a hydrophobic polymer, provides sustained release by forming a barrier that controls the diffusion of the drug (Wasilewska & Winnicka, 2019). Eudragit S-100, a pH-sensitive polymer, offers the advantage of targeted drug release in specific regions of the gastrointestinal tract (McCoubrey et al., 2023). The study sought to capitalize on their synergistic effects to optimize drug release kinetics and pellet properties by evaluating various combinations of these polymers. The choice of the polymer for the preparation of the pellets was based on the organoleptic characteristics of the pellets. Table 1 gives the results of this study.

| Trial number | Polymer or combination used | Drug:polymer ratio | Polymer:polymer ratio | Observation | %CR at the end of 12 hrs |
|---|---|---|---|---|---|
| F1 | HPMC | 2:1 | -- | Dough not formed | -- |
| F2 | HPMC | 1:1 | -- | Brittle exudates formed | -- |
| F3 | HPMC | 1:2 | -- | Sticky mass formed | -- |
| F4 | HPMC+EC | 1:1 | 2:1 | Sticky mass formed | -- |
| F5 | HPMC+EC | 1:1 | 1:1 | Pellets formed | 44.61 % |

| | | | | | |
|---|---|---|---|---|---|
| F6 | HPMC+EC | 1:1 | 1:2 | Pellets of good quality formed | 23.74 % |
| F7 | EC | 2:1 | -- | Pellets formed with rough surfaces | -- |
| F8 | EC | 1:1 | -- | Pellets formed | 25.41 % |
| F9 | EC | 1:2 | -- | Pellets formed | 12.48 % |
| F10 | EC + Eudragit S-100 | 1:1 | 2:1 | Pellets formed | 42.56 % |
| F11 | EC + Eudragit S-100 | 1:1 | 1:1 | Pellets formed | 47.23 % |
| F12 | EC + Eudragit S-100 | 1:1 | 1:2 | Pellets formed with rough surfaces | 51.82 % |
| F13 | Eudragit S-100 | 2:1 | -- | Pellets formed | 53.97 % |
| F14 | Eudragit S-100 | 1:1 | -- | Pellets formed | 53.84 % |
| F15 | Eudragit S-100 | 1:2 | -- | Pellets formed | 54.97 % |

The study aimed to optimize drug release kinetics and pellet properties by evaluating combinations of hydroxypropyl methylcellulose (HPMC) K4M, ethyl cellulose (EC), and Eudragit S-100 (S-100), well-established sustained-release agents in pharmaceutical formulations. HPMC, known for its film-forming properties and ability to modulate drug release through hydration and swelling, failed to form pellets efficiently in trials 1-3 due to issues like dough formation, brittle exudates, or sticky masses. Combining HPMC with EC (trials 4-6) improved pellet formation, with the 1:1 ratio yielding the best results, suggesting a synergistic effect between the two polymers. EC alone formed pellets with varying surface qualities depending on the ratio, indicating its influence on pellet morphology. Combining EC with S-100 (trials 10-12) produced pellets with improved drug release, with the 1:1 ratio showing the highest drug release percentage, indicative of the pH-sensitive nature of S-100 enhancing targeted drug release. S-100 alone showed excellent pellet formation irrespective of the ratio.

3.1.2 Selection of the concentration of the wetting agent

To enhance drug release from pellets, a wetting agent, sodium lauryl sulfate (SLS), was introduced to Batch F14 (Alshora et al., 2022). SLS concentrations of 1% and 2% by weight were employed. Results showed an increase in drug release to 66.67% and 67.22%, respectively, indicating the efficacy of SLS in improving drug release. However, the marginal difference between the two concentrations suggested that 1% SLS was optimal. Excessive SLS could potentially lead to micelle formation, which might hinder drug release by encapsulating the drug (Bahr et al., 2019). Thus, the study underscored the delicate balance required in wetting agent concentration to maximize drug release efficiency without inadvertently impeding it.

3.1.3 Modified sieving/spheronization technique

The study aimed to refine pellet preparation techniques to address challenges associated with material wastage and formulation yield optimization. Initially employing the extrusion/spheronization method, substantial material loss occurred due to adherence to the extruder, necessitating a shift to a sieving/spheronization approach. This modification involved meticulous ingredient weighing and dough formation utilizing water as a granulating solvent, followed by sieving to generate extrudates. These extrudates were then subjected to spheronization at 1000 rpm for 2-3 minutes, resulting in the formation of uniform, spherical pellets. Noteworthy was the efficiency of this method in accommodating batch sizes ranging from 4 to 5 grams, thereby minimizing material usage and associated losses. Experimentation with various sieve sizes, ranging from #8 to #36, revealed that sieve #22 consistently yielded pellets of optimal shape and size, demonstrating its suitability for the process. Despite achieving a significantly improved yield of 95% compared to the 50% obtained with extrusion, the drug release profile remained suboptimal (Theismann et al., 2019). Thus, while the modification in the pellet preparation technique proved beneficial in mitigating material wastage and improving yield, continued investigation and optimization are warranted to achieve the desired therapeutic outcomes.

3.2 Optimization of pellet formulation

The optimization of pellet formulation was conducted through nine trials based on the recommendations of DesignExpert® 13 software. Each trial varied in polymer proportion and binder concentration, with in vitro drug release and crushing strength serving as response variables. The details of the trials taken and the results obtained are shown in Table 1.

**Table 1: Details of the trials taken for the optimization of pellet formulation**

| Trial number | Polymer proportion (%) [A] | Binder concentration (mg) [B] | In vitro drug release (%) [Y1] | Crushing strength (kg) [Y2] |
|---|---|---|---|---|
| O1 | 33.33 | 100 | 63.58 | 2.75 |
| O2 | 50 | 50 | 67.29 | 2.08 |
| O3 | 33.33 | 200 | 59.46 | 3.48 |
| O4 | 50 | 100 | 64.58 | 3.45 |
| O5 | 50 | 200 | 55.98 | 6.48 |
| O6 | 66.66 | 100 | 43.68 | 6.28 |

| | | | | |
|---|---|---|---|---|
| O7 | 66.66 | 200 | 37.59 | 8.25 |
| O8 | 33.33 | 50 | 65.48 | 1.25 |
| O9 | 66.66 | 50 | 47.26 | 5.17 |

Analysis of variance (ANOVA) revealed that crushing strength adhered to a 2FI model with a p-value of 0.0011, exhibiting adjusted and predicted R2 values of 0.9210 and 0.8339, respectively. Conversely, in vitro drug release conformed to a quadratic model with a significant p-value of 0.0015, showing adjusted and predicted R2 values of 0.9843 and 0.9131, respectively. The coded equations for both responses were derived as follows: Crushing strength = 4.53 + 2.064A + 1.59B + 0.248AB, and In vitro drug release = 62.33 - 10.09A - 4.49B -0.88AB -9.77$A^2$ - 0.30$B^2$. Subsequently, 97 solutions were generated by the software to identify batches optimizing both in vitro drug release and crushing strength (within 2.5 to 4 kg). The first solution was scaled up, predicting a drug release of 68.146% and a crushing strength of 2.510 kg. Remarkably, the scaled-up batch demonstrated a release of 69.57 ± 3.56% and a crushing strength of 2.5 ± 0.2 kg, affirming the validity of the optimization parameters, experimental design, and resultant outcomes. The surface response plots for both responses have been shown in Figures 2 and 3. The final equation in the coded form for both responses was:

Crushing strength = 4.53 + 2.064A + 1.59B + 0.248AB

In vitro drug release = 62.33 - 10.09A -4.49B -0.88AB -9.77$A^2$ - 0.30$B^2$

Out of the 97 solutions generated by the software to optimize in vitro drug release while maintaining a crushing strength between 2.5 to 4 kg, the first solution was selected for scaling up. This solution was anticipated to exhibit a drug release of 68.146% alongside a crushing strength of 2.510 kg. Upon scaling up, the batch indeed demonstrated a drug release of 69.57 ± 3.56% and a crushing strength of 2.5 ± 0.2 kg. The remarkable proximity between predicted and observed results lends credibility to the selection of optimization parameters, experimental design, and the outcomes achieved.

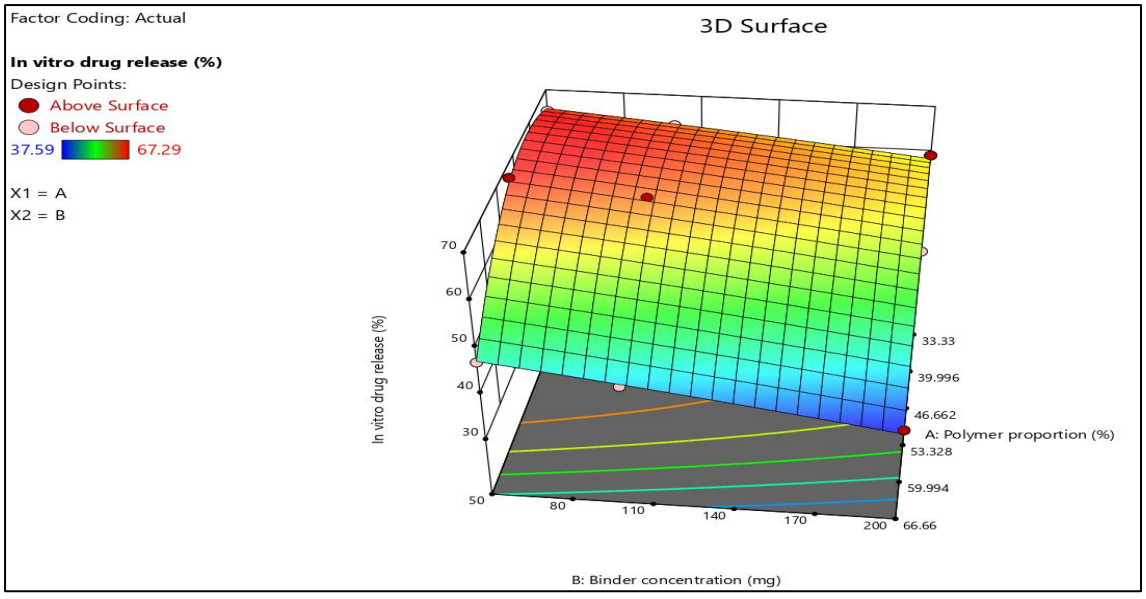


**Figure 2: 3D surface response plot for in vitro drug release (Y1)**

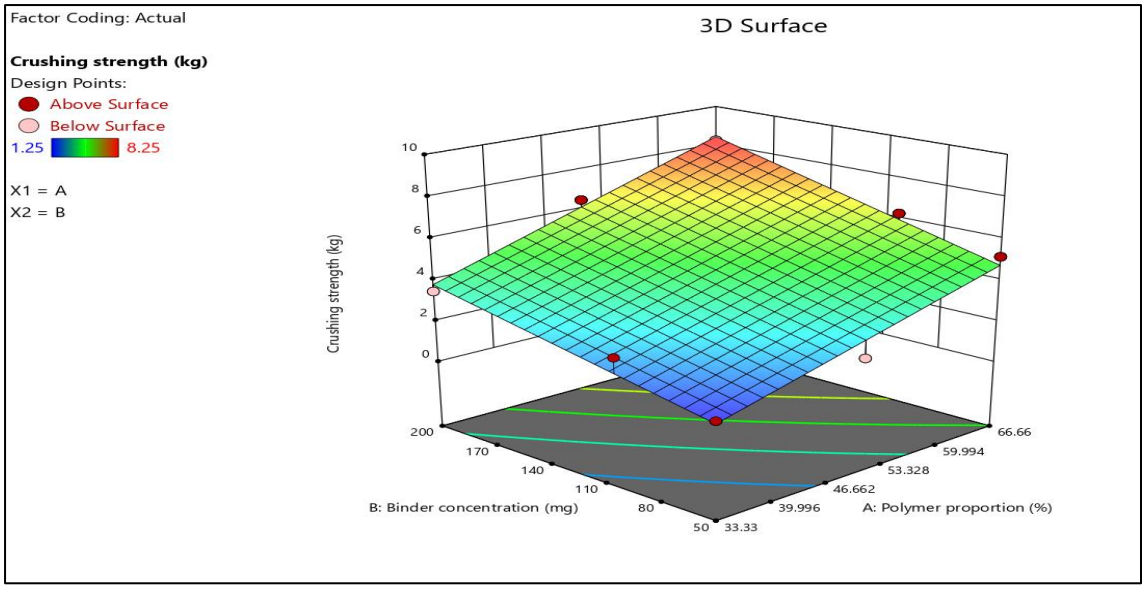


**Figure 3: 3D surface response plot for crushing strength (Y2)**

3.3 Evaluation of pellets

3.3.1 Morphological characterization

The morphological characterization of the pellets was conducted using Motic microscopy, with particle size analysis facilitated by Motic Images Plus 2.0 software. The examination revealed a mean particle size ranging from 600 µm to 900 µm for the pellets. This size range indicates uniformity in particle dimensions, suggesting consistency in the pellet manufacturing process. The representative image displayed in Figure 4 provides visual insight into the morphology of the pellets, illustrating their size and shape. The uniformity in particle size is essential for ensuring consistent drug release kinetics and dosing accuracy in pharmaceutical formulations. These results affirm the suitability of the pellet manufacturing process and highlight its potential for producing pellets with desired morphological attributes for pharmaceutical applications.

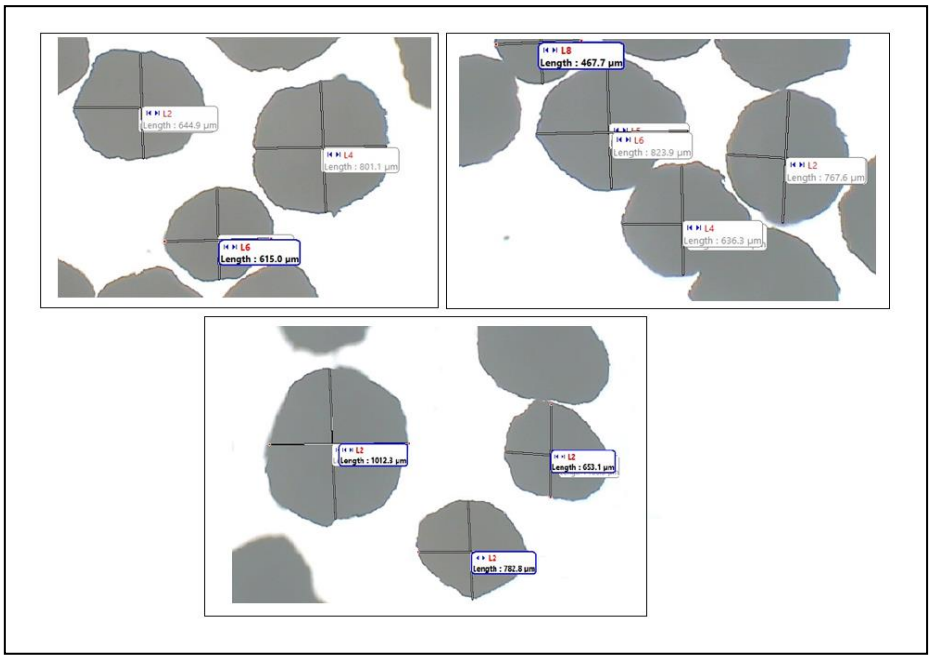


**Figure 4: Motic microscope scans of the scaled-up batch**

3.3.2 Assay

In this study, the assay of the scaled-up batch of pellets yielded a value of 97.62 ± 2.17 %. This result indicates the high level of drug content within the pellets, reflecting their efficacy in encapsulating and retaining the active pharmaceutical ingredient.

3.3.3 In vitro drug release profile and kinetics

The pellets were engineered with the specific objective of achieving biphasic drug release, characterized by an initial 30% release within the first hour, followed by a gradual release over the subsequent 11 hours. This intended release profile was successfully attained, wherein the initial burst release was attributed to the drug present on the pellet surface, while the entrapped drug exhibited a sustained release pattern over the extended duration. The release data underwent fitting to various kinetic models to elucidate the underlying mechanism of drug release. The selection of the most suitable model was predicated on the coefficient of correlation ($R^2$) values, with the highest $R^2$ value deemed indicative of the most appropriate model. Notably, the $R^2$ values obtained for the curve-fitting process were 0.9859 (Korsmeyer-Peppas model), 0.9967 (Higuchi square root model), 0.7908 (zero-order model), and 0.9421 (first-order model). Given the proximity of the $R^2$ value of the Higuchi square root model to unity, it was concluded as the optimal model for elucidating the drug release kinetics. This observation suggests that the drug release from the insoluble polymer matrix adheres to Fickian diffusion kinetics, wherein the release process is intricately linked to the square root of time (Mircioiu et al., 2019). Figure 5 gives the in vitro drug release profile of the drug from the scaled-up batch of the optimised pellets.

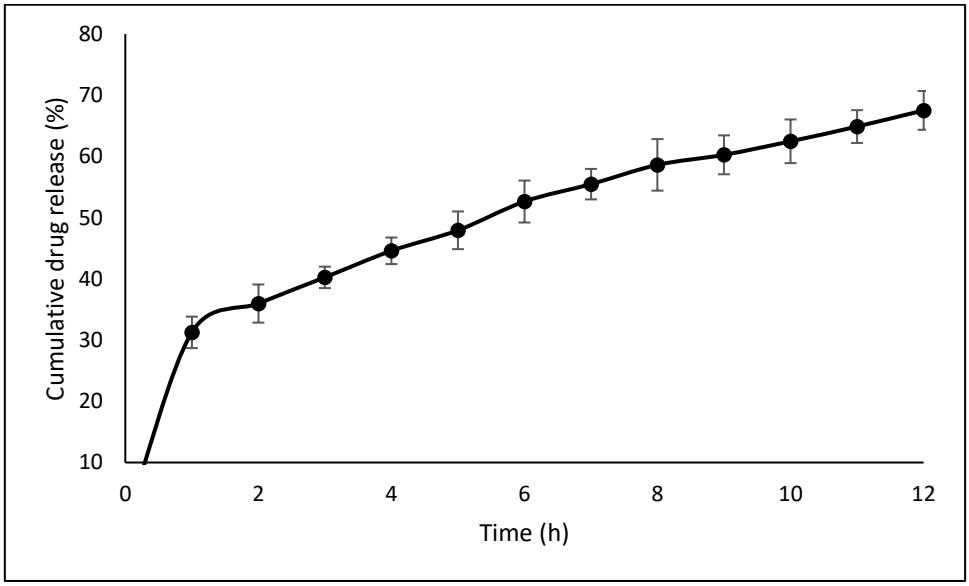


**Figure 5: In vitro drug release of diacerein from the optimized pellets**

## 4 Conclusion

In conclusion, the development of multiparticulate systems encapsulating diacerein within Eudragit beads via extrusion spheronization represents a promising advancement in osteoarthritis (OA) therapy. Through meticulous polymer selection, formulation optimization, and characterization, this study has demonstrated the feasibility and efficacy of the proposed

multiparticulate system in enhancing diacerein's solubility, stability, and therapeutic efficacy for OA management. The transition from extrusion/spheronization to sieving/spheronization techniques significantly reduced material wastage, improved formulation yield, and ensured the production of uniform, spherical pellets with enhanced drug release properties. Furthermore, optimization through DesignExpert® software facilitated the identification of formulation parameters conducive to achieving desired drug release kinetics and mechanical properties. The successful scaling up of the optimized batch validated the efficacy of the optimization approach, highlighting the potential of multiparticulate systems as a promising strategy for optimizing diacerein delivery in OA therapy, with future research avenues focusing on additional formulation refinements and preclinical efficacy assessments.

**5 References**

Ackerman, I. N., Bohensky, M. A., Zomer, E., Tacey, M., Gorelik, A., Brand, C. A., & de Steiger, R. (2019). The projected burden of primary total knee and hip replacement for osteoarthritis in Australia to the year 2030. *BMC Musculoskeletal Disorders*, *20*(1), 90. https://doi.org/10.1186/s12891-019-2411-9

Allam, A. N., Hamdallah, S. I., & Abdallah, O. Y. (2017). Chitosan-coated diacerein nanosuspensions as a platform for enhancing bioavailability and lowering side effects: Preparation, characterization, and ex vivo/in vivo evaluation. *International Journal of Nanomedicine*, *12*, 4733–4745. https://doi.org/10.2147/IJN.S139706

Alshora, D. H., Ibrahim, M. A., Zayed, G., Al Rwashed, M. A., Abou-Taleb, H. A., & Ali, M. F. (2022). The role of sodium lauryl sulfate on formulation of directly compressed tablets containing simvastatin and aspirin: Effect on drugs dissolution and gastric mucosa. *Saudi Pharmaceutical Journal*, *30*(5), 635–645. https://doi.org/10.1016/j.jsps.2022.02.006

Bahr, M. N., Modi, D., Patel, S., Campbell, G., & Stockdale, G. (2019). Understanding the Role of Sodium Lauryl Sulfate on the Biorelevant Solubility of a Combination of Poorly Water-Soluble Drugs Using High Throughput Experimentation and Mechanistic Absorption Modeling. *Journal of Pharmacy & Pharmaceutical Sciences: A Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne Des Sciences Pharmaceutiques*, *22*(1), 221–246. https://doi.org/10.18433/jpps30347

Batt, D. K., & Garala, K. C. (2013). Preparation and evaluation of inclusion complexes of diacerein with β-cyclodextrin and hydroxypropyl β-cyclodextrin. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *77*(1), 471–481. https://doi.org/10.1007/s10847-012-0268-8

Bruschi, M. L. (Ed.). (2015). 5—Mathematical models of drug release. In *Strategies to Modify the Drug Release from Pharmaceutical Systems* (pp. 63–86). Woodhead Publishing. https://doi.org/10.1016/B978-0-08-100092-2.00005-9

Costa, B. R. da, Pereira, T. V., Saadat, P., Rudnicki, M., Iskander, S. M., Bodmer, N. S., Bobos, P., Gao, L., Kiyomoto, H. D., Montezuma, T., Almeida, M. O., Cheng, P.-S., Hincapié, C. A., Hari, R., Sutton, A. J., Tugwell, P., Hawker, G. A., & Jüni, P. (2021). Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: Network meta-analysis. *BMJ*, *375*, n2321. https://doi.org/10.1136/bmj.n2321

dos Santos, J., da Silva, G. S., Velho, M. C., & Beck, R. C. R. (2021). Eudragit®: A Versatile Family of Polymers for Hot Melt Extrusion and 3D Printing Processes in Pharmaceutics. *Pharmaceutics*, *13*(9), 1424. https://doi.org/10.3390/pharmaceutics13091424

El-Laithy, H. M., Basalious, E. B., El-Hoseiny, B. M., & Adel, M. M. (2015). Novel self-nanoemulsifying self-nanosuspension (SNESNS) for enhancing oral bioavailability of diacerein: Simultaneous portal blood absorption and lymphatic delivery. *International Journal of Pharmaceutics*, *490*(1), 146–154. https://doi.org/10.1016/j.ijpharm.2015.05.039

El-Say, K. M., Abd-Allah, F. I., Lila, A. E., Hassan, A. E.-S. A., & Kassem, A. E. A. (2016). Diacerein niosomal gel for topical delivery: Development, in vitro and in vivo assessment. *Journal of Liposome Research*, *26*(1), 57–68. https://doi.org/10.3109/08982104.2015.1029495

Fouad, S. A., Malaak, F. A., El-Nabarawi, M. A., Abu Zeid, K., & Ghoneim, A. M. (2021). Preparation of solid dispersion systems for enhanced dissolution of poorly water soluble diacerein: In-vitro evaluation, optimization and physiologically based pharmacokinetic modeling. *PLoS ONE*, *16*(1), e0245482. https://doi.org/10.1371/journal.pone.0245482

He, Y., Li, Z., Alexander, P. G., Ocasio-Nieves, B. D., Yocum, L., Lin, H., & Tuan, R. S. (2020). Pathogenesis of Osteoarthritis: Risk Factors, Regulatory Pathways in Chondrocytes, and Experimental Models. *Biology*, *9*(8), 194. https://doi.org/10.3390/biology9080194

Hiew, T. N., Tian, Y. H., Tan, H. M., & Heng, P. W. S. (2020). A mechanistic understanding of compression damage to the dissolubility of coated pellets in tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *146*, 93–100. https://doi.org/10.1016/j.ejpb.2019.11.006

Jain, A., Singh, S. K., Singh, Y., & Singh, S. (2013). Development of lipid nanoparticles of diacerein, an antiosteoarthritic drug for enhancement in bioavailability and reduction in its side effects. *Journal of Biomedical Nanotechnology*, *9*(5), 891–900. https://doi.org/10.1166/jbn.2013.1580

Kaur, V., Goyal, A. K., Ghosh, G., Si, S. C., & Rath, G. (2020). Development and characterization of pellets for targeted delivery of 5-fluorouracil and phytic acid for treatment of colon cancer in Wistar rat. *Heliyon*, *6*(1). https://doi.org/10.1016/j.heliyon.2019.e03125

Komati, S., Swain, S., Rao, M. E. B., Jena, B. R., & Dasi, V. (2019). Mucoadhesive Multiparticulate Drug Delivery Systems: An Extensive Review of Patents. *Advanced Pharmaceutical Bulletin*, *9*(4), 521–538. https://doi.org/10.15171/apb.2019.062

Kongtharvonskul, J., Woratanarat, P., McEvoy, M., Attia, J., Wongsak, S., Kawinwonggowit, V., & Thakkinstian, A. (2016). Efficacy of glucosamine plus diacerein versus monotherapy of glucosamine: A double-blind, parallel randomized clinical trial. *Arthritis Research & Therapy*, *18*(1), 233. https://doi.org/10.1186/s13075-016-1124-9

Liu, L., Tang, H., & Wang, Y. (2023). Polymeric biomaterials: Advanced drug delivery systems in osteoarthritis treatment. *Heliyon*, *9*(11), e21544. https://doi.org/10.1016/j.heliyon.2023.e21544

Maboos, M., Yousuf, R. I., Shoaib, M. H., Nasiri, I., Hussain, T., Ahmed, H. F., & Iffat, W. (2018). Effect of lipid and cellulose based matrix former on the release of highly soluble drug from extruded/spheronized, sintered and compacted pellets. *Lipids in Health and Disease*, *17*, 136. https://doi.org/10.1186/s12944-018-0783-8

Mallipeddi, R., Saripella, K. K., & Neau, S. H. (2014). Use of fine particle ethylcellulose as the diluent in the production of pellets by extrusion-spheronization. *Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society*, *22*(4), 360–372. https://doi.org/10.1016/j.jsps.2013.11.001

McCoubrey, L. E., Favaron, A., Awad, A., Orlu, M., Gaisford, S., & Basit, A. W. (2023). Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *Journal of Controlled Release*, *353*, 1107–1126. https://doi.org/10.1016/j.jconrel.2022.12.029

Mircioiu, C., Voicu, V., Anuta, V., Tudose, A., Celia, C., Paolino, D., Fresta, M., Sandulovici, R., & Mircioiu, I. (2019). Mathematical Modeling of Release Kinetics from Supramolecular Drug Delivery Systems. *Pharmaceutics*, *11*(3), 140. https://doi.org/10.3390/pharmaceutics11030140

Muley, S., Nandgude, T., & Poddar, S. (2016). Extrusion–spheronization a promising pelletization technique: In-depth review. *Asian Journal of Pharmaceutical Sciences*, *11*(6), 684–699. https://doi.org/10.1016/j.ajps.2016.08.001

Nikam, A., Sahoo, P. R., Musale, S., Pagar, R. R., Paiva-Santos, A. C., & Giram, P. S. (2023). A Systematic Overview of Eudragit® Based Copolymer for Smart Healthcare. *Pharmaceutics*, *15*(2), 587. https://doi.org/10.3390/pharmaceutics15020587

Pan, P., Svirskis, D., Waterhouse, G. I. N., & Wu, Z. (2023). Hydroxypropyl Methylcellulose Bioadhesive Hydrogels for Topical Application and Sustained Drug Release: The Effect of Polyvinylpyrrolidone on the Physicomechanical Properties of Hydrogel. *Pharmaceutics*, *15*(9), Article 9. https://doi.org/10.3390/pharmaceutics15092360

Pande, V. V., Sanklecha, V. M., Arote, S. R., & Department of Pharmaceutics (PG), Sanjivani College of Pharmaceutical Education and Research, Kopargaon - 423 603, Maharashtra, India. (2019). Formulation and development of extended release matrix pellets of water insoluble azilsartan medoxomil with solid dispersion. *INDIAN DRUGS*, *56*(02), 21–30. https://doi.org/10.53879/id.56.02.11671

Patil, S. B., Shete, D. K., Narade, S. B., Surve, S. S., Khan, Z. K., Bhise, S. B., & Pore, Y. V. (2010). Improvement in the dissolution profile of diacerein using a surfactant-based solid dispersion technique. *Drug Discoveries & Therapeutics*, *4*(6), 435–441.

Pavelka, K., Bruyère, O., Cooper, C., Kanis, J. A., Leeb, B. F., Maheu, E., Martel-Pelletier, J., Monfort, J., Pelletier, J.-P., Rizzoli, R., & Reginster, J.-Y. (2016). Diacerein: Benefits, Risks and Place in the Management of Osteoarthritis. An Opinion-Based Report from the ESCEO. *Drugs & Aging*, *33*(2), 75–85. https://doi.org/10.1007/s40266-016-0347-4

Priese, F., Wiegel, D., Funaro, C., Mondelli, G., & Wolf, B. (2023). Comparison of Mini-Tablets and Pellets as Multiparticulate Drug Delivery Systems for Controlled Drug Release. *Coatings*, *13*(11), Article 11. https://doi.org/10.3390/coatings13111891

Silva, R. C. L., Sasso-Cerri, E., & Cerri, P. S. (2022). Diacerein-induced interleukin-1β deficiency reduces the inflammatory infiltrate and immunoexpression of matrix

metalloproteinase-8 in periodontitis in rat molars. *Journal of Periodontology*, *93*(10), 1540–1552. https://doi.org/10.1002/JPER.21-0375

Sirikaew, N., Chomdej, S., Tangyuenyong, S., Tangjitjaroen, W., Somgird, C., Thitaram, C., & Ongchai, S. (2019). Proinflammatory cytokines and lipopolysaccharides up regulate MMP-3 and MMP-13 production in Asian elephant (Elephas maximus) chondrocytes: Attenuation by anti-arthritic agents. *BMC Veterinary Research*, *15*(1), 419. https://doi.org/10.1186/s12917-019-2170-8

Steinmetz, J. D., Culbreth, G. T., Haile, L. M., Rafferty, Q., Lo, J., Fukutaki, K. G., Cruz, J. A., Smith, A. E., Vollset, S. E., Brooks, P. M., Cross, M., Woolf, A. D., Hagins, H., Abbasi-Kangevari, M., Abedi, A., Ackerman, I. N., Amu, H., Antony, B., Arabloo, J., … Kopec, J. A. (2023). Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: A systematic analysis for the Global Burden of Disease Study 2021. *The Lancet Rheumatology*, *5*(9), e508–e522. https://doi.org/10.1016/S2665-9913(23)00163-7

Theismann, E.-M., K. Keppler, J., Owen, M., Schwarz, K., & Schlindwein, W. (2019). Modelling the Effect of Process Parameters on the Wet Extrusion and Spheronisation of High-Loaded Nicotinamide Pellets Using a Quality by Design Approach. *Pharmaceutics*, *11*(4), Article 4. https://doi.org/10.3390/pharmaceutics11040154

Timur, U. T., Caron, M. M. J., Jeuken, R. M., Bastiaansen-Jenniskens, Y. M., Welting, T. J. M., van Rhijn, L. W., van Osch, G. J. V. M., & Emans, P. J. (2020). Chondroprotective Actions of Selective COX-2 Inhibitors In Vivo: A Systematic Review. *International Journal of Molecular Sciences*, *21*(18), Article 18. https://doi.org/10.3390/ijms21186962

Wasilewska, K., & Winnicka, K. (2019). Ethylcellulose–A Pharmaceutical Excipient with Multidirectional Application in Drug Dosage Forms Development. *Materials*, *12*(20). https://doi.org/10.3390/ma12203386

Young, J. J., Pedersen, J. R., & Bricca, A. (2023). Exercise Therapy for Knee and Hip Osteoarthritis: Is There An Ideal Prescription? *Current Treatment Options in Rheumatology*, *9*(3), 82–98. https://doi.org/10.1007/s40674-023-00205-z

Zeng, F., Wang, K., Duan, H., Xu, X., Kuang, G., & Lu, M. (2023). Diacerein versus non-steroidal anti-inflammatory drugs in the treatment of knee osteoarthritis: A meta-analysis. *Journal of Orthopaedic Surgery and Research*, *18*, 308. https://doi.org/10.1186/s13018-023-03786-6