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Recent Advancements and Future Perspectives in Diacerein Delivery Systems for Rheumatoid Arthritis: Novel Strategies and Emerging Technologies

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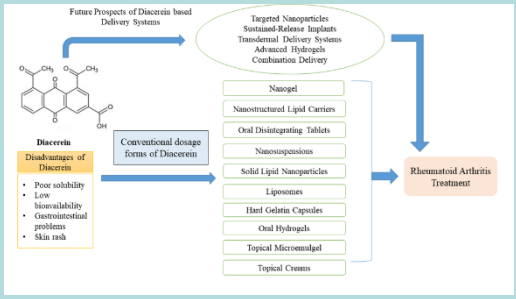
Abstract: For the treatment of Rheumatoid Arthritis, Diacerein, an anthraquinone derivative, is known for its chondroprotective and anti-inflammatory properties. It has the potential to be therapeutic, however, its clinical value is limited by factors like poor solubility, low bioavailability, and gastrointestinal adverse effects. An extensive summary of cutting-edge delivery strategies created to improve the effectiveness of Diacerein, and patient adherence is given in this review. These delivery techniques include transdermal patches for non-invasive administration, liposomes and nanoparticles for enhanced bioavailability and targeted distribution, topical gels for localized treatment, and oral tablets with modified-release formulations. Furthermore, new technologies promising for regulated and sustained release include hydrogel-based systems microneedles, etc. The assessment also looks at the field's possibility from now on, highlighting the necessity of using improved biomaterials including carriers of medications in personalized medical techniques. Future research attempts to maximize the therapeutic profile of Diacerein, better Rheumatoid Arthritis management, and improve patient outcomes by resolving present issues and utilizing cutting-edge technologies. Realizing these objectives will depend heavily on existing clinical studies and technological developments. This review aims to better understand Diacerein's conventional formulations and comprehend their future improvement.



Keywords: Diacerein, Rheumatoid Arthritis, Drug Delivery Systems, Bioavailability, Nanotechnology, Patient Adherence.

Introduction

Diacerein is mainly used in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), psoriasis, and epidermolysis bullosa for its anti-inflammatory properties [1, 2]. It is an anthraquinone group of drugs that mainly acts by its active metabolite Rhein (Figure 1) [3,4].

Chemical Structure of diacerein, or 4,5-bis(acetoxy)-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid [5], is a member of the family of small compounds called anthraquinones [6]. Its molar mass is 368.29 g/mol, and the chemical formula is $C_{19}H_{12}O_6$ [7,8]. Diacerein's structure has a planar anthracene core [9,10], and a tricyclic aromatic hydrocarbon framework comprising three fused benzene rings [11,12]. The anthracene ring's structure 2-position is where a carboxylic acid group attaches [13]. The dioxo-9,10-dihydroanthracene moiety of the anthraquinone core is defined by two keto groups at positions 9 and 10 [14,15]. Furthermore, at positions 4 and 5, the molecule's anthracene ring is joined to the two acetoxy groups (-$OCOCH_3$) [16,17,18].

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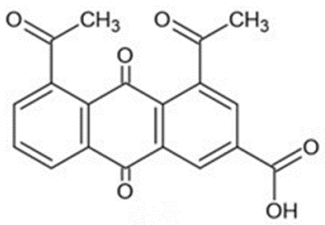

Molecular Formula- $C_{19}H_{12}O_6$; Formula Weight- 336.299
IUPAC Name- 4,5-diacetyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid

Figure (1): Chemical structure of Diacerein.

Diacerein is converted to its active metabolite Rhein by deacetylation reaction [19]. The drug acts by inhibiting of Interleukin (IL)-1β biosynthetic pathway, inhibiting the enzyme IL-1β converting enzyme [20], which catalyzes the conversion of Pro- IL-1β to IL-1β [21]. Thus, IL-1β-mediated deleterious effects in RA are inhibited by diacerein [22]. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are two more inflammatory cytokines that diacerein indirectly inhibits by decreasing IL-1β activity [23,24]. This reduces joint swelling and synovial inflammation by downregulating inflammatory signalling pathways (Figure 2) [25,26,27]. Additionally, cartilage is shielded from further deterioration by diacerein, which suppresses matrix metalloproteinases (MMPs) [28], which are enzymes that break down the components of the cartilage matrix [29,30]. This anti-inflammatory and cartilage-preserving activity helps to delay the progression of the condition [31]. Apart from this, diacerein directly increases the expression of Transforming Growth Factor (TGF)-1 and (TGF)-2 which is required for proper growth of cartilage [32,33]. Chondrocyte surface expression of IL-1β receptors is decreased by the drug, while it increases IL-1 receptor antagonism [34].

Diacerein belongs to BCS class II drugs exhibiting low aqueous solubility which results in reduced and variable bioavailability (35%- 56%) [35]. The most frequent adverse drug reaction associated with oral diacerein therapy are diarrhoea, soft stool, and hepatotoxicity [36], which significantly reduces patient compliance [37]. So, improving bioavailability and reducing adverse effects is an important approach for diacerein therapy in managing previously mentioned diseases.

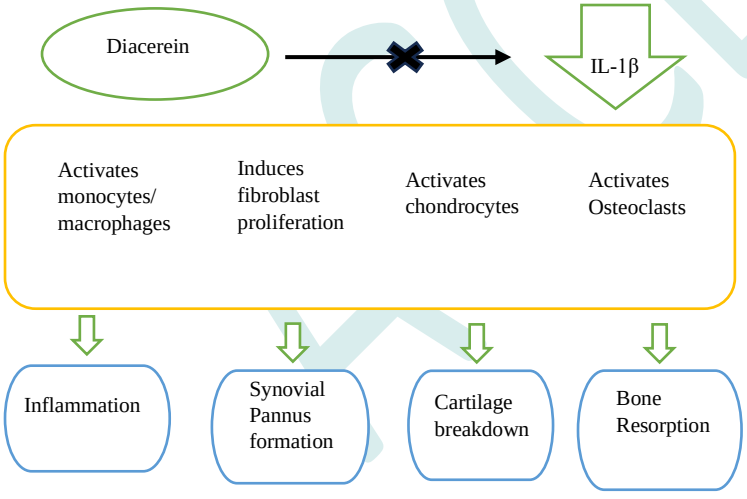

Figure (2): Summary of Diacerein inhibiting IL-1β.

This review provides a detailed view of the various types of established diacerein formulations, focusing on their advantages and disadvantages and a brief view of their preparation. It also provides ideas about formulations that can be prepared in the future to nullify the adverse effects of the proven formulations.

2A. Various types of investigated dosage forms of Diacerein by oral route of administration

Investigated oral drug delivery systems of diacerein provide many advantages such as therapy effects occurring more quickly in the oral mucosa when there is rapid breakdown and absorption, increased diacerein bioavailability by preventing degradation and guaranteeing a steady release, prevented peaks and fluctuations that may result in decreased effectiveness by maintaining more constant plasma concentrations. Alongside advantages, many disadvantages were also reported like reduced and irregular absorption as a result of a delayed gastrointestinal transit time known as variable absorption, restricted ability to load drugs, potential for gastrointestinal discomfort as a result of the drug's extended residence in the GI system is one of the side effects related to digestion [38].

For the formulation of Buccal Tablets, it was reported that the methodology direct compression method was used, and the powder mix was pressed into tablets using bioadhesive polymers Gum Karaya, Sodium Alginate, Carbopol 974P, and Carbopol 941NF in varying ratios. The *in vitro* drug release of 99.59% was attained with the improved formulation. From the results of the measurement of *ex vivo* bioadhesive strength, every polymer has a threshold concentration, above which its highly coiled structure causes it to form an undisturbed state. Consequently, the solvent's accessibility to the polymer declines, and the polymer's chain penetration significantly diminishes [39].

In the development of Expandable tablet formulation, the methodology employed was the wet granulation method. The hydrophilic swellable polymers polyethylene oxide and Hydroxypropylmethylcellulose (HPMC) K100 and the hydrophobic polymers Carbopol 934 and Chitosan, carboxymethyl cellulose (CMC), were used to formulate expandable gastroretentive tablets of diacerein. *In vitro* drug release study showed 94.4% drug release in 24 hours and encapsulation efficiency (%EE) was found to be 99.10% for the optimized formulation. This formulation required a temperature of 25ºC ± 2ºC. Temperature higher than this resulted in a reduction of drug content as well as variations in hardness and appearance were also observed [40].

Lactose monohydrate and diacerein were combined in a double-cone blender by the wet granulation method employed for the formulation of Hard Gelatin Capsules. Size "1" firm gelatin capsules with an off-white body and a yellow opaque lid were used to hold these granules. Equivalency in dissolution kinetics was confirmed by similarity factor values, which varied from 50 to 100. It was discovered that diacerein is nearly insoluble in a buffer solution with a pH of 1.2, includes a low solubility in a buffer solution with a pH of 4.5, and becomes more soluble as the medium's pH rises to 6.8 [41].

Table (1) provides the methods, advantages, and drawbacks of the studied dosage form based on diacerein, depending on the oral route of administration.

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Sl. No	Formulations	Methodology	Outcomes	Advantages and Drawbacks	Ref.
1.	**Binary Solid Lipid Nanoparticles (SLNs)**	Hot Melt Encapsulation was used to create microemulsion and the organic phase was	Both diacerein-loaded SLNs and those concurrentl y packed	**Advantages-** Binary SLNs' thermo-responsive potential analysis revealed that the release of the whole medication occurs over 72 hours at 37°C. When high body	[42]

		made by evaporating binary fatty acid combinations and lecithin into chloroform using the solvent emulsification evaporation technique.	with gold nanoparticles (GNPs) demonstrated high %EE. The addition of GNPs shortened the release period, but an enhanced diacerein payload prolonged it.	temperatures occur under different clinical circumstances, the sustained release profile of diacerein at physiological body temperature might change to an instantaneous release pattern. **Drawbacks-** Stearic acid and oleic acid at 2:1 had a melting point of 41°C, but because of the increased oleic acid concentration, it was not appropriate for SLN formulation since it formed oil clusters and was less stable.	
2.	**Buccal Strips**	The solvent casting procedure was applied with varying ratios of poloxamer 407. Double-distilled water was used to prepare the polymeric solutions, which were continuously stirred.	The formulation showed a 54-second disintegration time, a 97.74% dissolve rate at 2 minutes, and a drug release of 97.44% in 70 minutes.	**Advantages-** The formulations' surface pH ranged from 6.2 to 6.8, indicating that the oral buccal mucosa was not irritated, and their mucoadhesive retention duration was between 6.5 and 8.2 hours. **Drawbacks-** The absorption investigation revealed that a strip's resistance to moisture fluctuations was below ideal, which might lead to the strip's inconsistent adherence to the buccal mucosa.	[43]
3.	**Cocrystals**	The solvent and the liquid-assisted grinding approach were done. Three cocrystals of diacerein were created with iso-nicotinamide (ISO), nicotinamide (NIC), and	Diacerein-ISO cocrystal showed a 3.2-fold increase in the bio-availability. The cocrystals diacerein-NIC, diacerein-ISO, and	**Advantages-** The cocrystals' superior water solubility and improved *in vivo* drug absorption were justified by the increased plasma concentration of diacerein in them. When compared to free diacerein, the cocrystals' relative bioavailability produced better outcomes. **Drawbacks-** A single crystal of the right size for	[44]

		theophylline (THE). The solvent drop grinding process was used to create each cocrystal.	diacerein-THE have relative bio-availabilities of 3.45, 2.35, and 1.69 times the parent drug, indicating improved *in vivo* absorption of the drug.	single-crystal X-ray diffraction (XRD) was not achieved despite many attempts to recrystallize the created cocrystals from acceptable solvents.	
4.	**Fatty Acid–Based Self-Emulsifying Solid Dispersions**	The fusion process was performed. Drug: PEG6000: Tween80 ternary solid dispersions (SDs) were made in weight ratios of 50:50:0.5 (SD1) and 50:50:1 (SD2). The bulk was kept in a desiccator above-fused calcium chloride.	The optimized solid dispersion of diacerein increased the dissolving efficiency by 10.83 times at 15 minutes and by 3.42 times at 60 minutes. *In vitro* drug release was found to be 90.6%.	**Advantages-** When exposed to an aqueous medium, the use of a surfactant and a fatty acid and surfactant combination in PEG 6000-based SD is a helpful technique to increase the *in vitro* dissolution rate of diacerein that is weakly water-soluble by creating solubilizing and microemulsifying systems. **Drawbacks-** There was a lack of a drug melting peak in the Differential Scanning Calorimetry (DSC) spectra in the ternary SDs and microemulsifying SDs and the reduction in intensity of the drug's many unique peaks in the Powder X-ray diffractograms (PXRD) spectra.	[45]
5.	**Film-Coated Pulsatile Release Tablet**	The direct compression approach was used to create cores having diacerein, with croscarmellose sodium acting	During the first 120 minutes, the formulations did not exhibit any drug release in acidic	**Advantages-** From the *in vitro* study, it can be concluded that diacerein's film-coated tablet synchronizes medication release with the body's circadian cycles. Therefore, it can be	[46]

		as a super disintegrant. Triethylcitrate was used as a plasticizer and Eudragit S100 and L100 as polymers to create the coating solution.	conditions; however, after switching to a pH 6.8 buffer, there was a noticeable release. *In vitro* drug release was observed to be 90% at 5.5 hours.	administered before bed since it postpones the release of the medicine in the morning when arthritic pains are more prevalent. **Drawbacks-** The decreased level of croscarmellose sodium created a reduction in drug release, whereas, increasing the amount caused the improper coating of the film.	
6.	**Oral Hydrogels**	Potassium per sulfate, acrylic acid, and the cross-linker methylene bisacrylamide was added together to create a solution. After the clear solution had been set, the hydrogels were taken out and trimmed to a 5 mm length.	The findings demonstrated that every hydrogel formulation is sensitive to pH and releases drugs according to zero-order kinetics.	**Advantages-** The hydrogel sample has voids, according to the Scanning Electron Microscopy (SEM) analysis, which lets the medication attach to the interpenetrating hydrogels as much as feasible. **Drawbacks-** The prepared hydrogels showed extreme sensitivity to changes in pH. A slight change in pH resulted in uneven drug distribution.	[47]
7.	**Liposomes (LPS)**	Diacerein and Tyr-3-octreotide, a somatostatin analog (SST), were used to construct the liposomes. The SST analog was linearly conjugated with 1,2-Bis (diphenylphosphino) ethane, a lipid moiety, and a PEG linker.	Diacerein-loaded liposomes (DNL) and SST-DNL had %EE of around 86% and 82%. According to the cumulative drug release analysis, the DNL and SST-DNL groups released approx.	**Advantages-** SST-DNL demonstrated strong antiangiogenic and anti-invasive properties against cancer cells. Additionally, SST-DNL therapy significantly changed 367 oncogenic IL-6/IL-6R signaling pathways and several pro/anti-apoptotic proteins. **Drawbacks-** The Fourier Transfer Infrared Spectroscopy (FTIR) analysis revealed little interaction between the excipients and diacerein	[48]

			56% and 54% of the total amount of diacerein after 24 hours.	in the form of a hydrogen bond. Since SST pre-treatment blocked the SSTR2 receptor, SST-DNL was unable to use that receptor to target cancer cells. Thus, SST-DNL's anti-proliferative impact was diminished.	
8.	**Microspheres**	To provide sustained-release medication delivery, HPMC and ethyl cellulose were used as release-delaying polymers in the Wurster method of spray coating to create diacerein-loaded microspheres.	The *in vitro* drug release study showed about 80% drug was released at 24 hours in a phosphate buffer of pH 6.8. In citrate buffer, about 65% of the drug was released at 24 hours.	**Advantages-** SEM analysis reveals the development of holes that might allow a solvent to enter, causing the internal matrix to inflate and releasing the medication by burst release. The development of pores indicates that the diffusion mechanism oversees the prolonged release. **Drawbacks-** A slight change was observed in the physical mixture of diacerein and other components from the XRD report which resulted in diacerein's purity being reduced during microsphere creation.	[49]
9.	**Nanofibers**	The Poly L-lactic acid (PLLA) solution was dissolved in a 4/1 mixture of chloroform and dimethyl formamide. Diacerein was then added to the polymer solution. For electro-spinning, a 5 mL syringe was filled with 5 mL of the	It was found that the nanofiber patch had an 89.47% drug content. 61.3% of the medication was released in 30 hours, according to the *in vitro* drug release graph.	**Advantages-** The increased surface area of the nanofibers may have contributed to the first burst release of around 15% during the first hour of the trial. This was followed by a regulated release of the medication from the core of the nanofibers. **Drawbacks-** The formulation had a relatively low tensile strength since the mechanical durability of fibers is inversely related to their diameter, the tiny	[50]

		polymer/drug solution, and the injection rate was set at 0.04 ml/hr.	Drug-loaded PLLA nanofibers had a tensile strength of 29 g/cm2.	fiber diameter of blank nanofibers accounts for their high tensile strength value.	
10.	**Nano-suspension**	Diacerein was produced as an aqueous nano-suspension by combining the High-Speed Homo-genization and Media Milling techniques. As a stabilizer, 1% of the drug's concentration of poloxamer 407 was utilized.	The cumulative percentage of drug release was 97.74% in 2 minutes compared to the unmilled drug results of 43.42% over 20 minutes noted following drug nanosizing.	**Advantages-**Compared to the unmilled drug suspension, the produced nano-suspension dissolved much more quickly in dissolving medium *in vitro*. This suggests that diacerein nano-suspension enhances both dissolution and saturation solubility, potentially increasing the drug's oral bioavailability. **Drawbacks-** From the stability investigation, the formulation was kept for a month at 40 ± 2°C and 75 ± 5% relative humidity. All the optimization parameters were found to have changed slightly, with a bias of less than ±5%.	[51]
11.	**Oral Dissolving Films (ODFs)**	The solvent casting procedure was used to create the diacerein ODFs. HPMC, sodium alginate, Guar gum, sodium crosmellose, gelatin were agitated for 20 minutes at 1000 rpm with glycerol using a magnetic stirrer.	The dissolving behavior was found 99.688% in 3 minutes, and a quick *in-vitro* disintegratio n time of 13 seconds. The drug concentratio n in films ranged from 99.94% to 96.32%.	**Advantages-** From the results of *in vitro* disintegration time, ODFs of diacerein may therefore provide immediate osteoarthritis relief with improved patient compliance. **Drawbacks-** Solubility studies revealed that at greater concentrations, β cyclodextrin gradually increased the solubility of diacerein; however, this also caused the formulation to become more hygroscopic and unstable.	[52]
12.	**Oral Disintegrating**	Diacerein-ODTs were	In dissolving	**Advantages-** When compared to the	[53]

	Tablets (ODTs)	made utilizing the technique of direct compression. It included 1:4 w/w of diacerein and PEG 8000. Then the pre-made, co-processed excipients in varying proportions to the previously generated optimum diacerein-solid dispersion.	medium, ODTs based on diacerein demonstrated 80–95% drug release in the first half hour. The produced pills' mean diacerein concentration varied between 96.19 ± 2.34% and 101.23 ± 0.78%.	commercial formulation, the rat paw edema model's *in vivo* anti-inflammatory effectiveness verified the notable inhibition of edema at 0.5 hours. **Drawbacks-** It was found that the formulations containing just one type of co-processed excipients employed went over the permissible disintegration time (>180 s).	
13.	**Press-Coated Pulsatile Release Tablet**	Diacerein, polyvinylpyrrolidone (PVP K30), micro-crystalline cellulose, sodium starch glycolate, magnesium stearate, and talc were weighed and then passed through a 60 # sieve. A rotary tablet compression machine was used to compress this powder combination using a 6 mm punch.	The press-coated tablets had a lag time of 6 hours before the release started. Nearly all of the drug was released quickly within 1-2 hours after the lag time when the release profile changed to an instant release phase.	**Advantages-** From the results, drug release lag time for diacerein at the first hour, a press-coated tablet synchronizes drug release with the body's circadian cycles. It can thus be given before bed since it delays the onset of the medication's release in the early morning when arthritic attacks are more likely to occur, and this mode of drug administration can offer sufficient defense against them. **Drawbacks-** The amount of diacerein release decreased along with the quantity of starch glycolate which is the swellable disintegrant.	[54]
14.	**Proliposomes (PLs)**	PLs with diacerein were made using constant quantities of maltodextrin	Diacerein PLs demonstrated a delayed drug release of 46.7%	**Advantages-** The absence of a distinctive peak across the diacerein melting point range in the formulations indicates that the medication was	[55]

		and different ratios of soy and egg lecithin to cholesterol. The thin layer hydration process was used to prepare PLs.	after 12 hours and an %EE of 91.13% ± 2.25%.	successfully entrapped amid the vesicles and that its crystalline form had changed into an amorphous form. **Drawbacks-** The PXRD study showed that few crystalline peaks were observed, which proves the entire transition of diacerein from crystalline to amorphous form did not take place.	
15.	**Solid Dispersions**	Spray drying was used to create diacerein-based solid dis persions. After dissolving 20 g of diacerein in DMSO, acetonitrile was added. After that, Aerosil was added to the mixture to dilute it, and it was stirred.	90% of drug release was observed in the *in vitro* drug release study. Permeation efficiency of 90% was studied from the results.	**Advantages-** *In vitro* drug release study showed that spray drying has been shown to boost the pace of drug dissolution by improving wetting and reducing particle aggregation tendencies, which in turn speeds up drug release. **Drawbacks-** The dissolution of weakly water-soluble diacerein is significantly influenced by the swelling capacity of Guar gum. Guar gum's hydrophilic properties alter the hydrodynamic environment surrounding the formulation, which slows down the rate of fast drug release.	[56]
16.	**Solid Self-Micro-Emulsifying Drug Delivery System (S-SMEDDS)**	Oleic acid was added to diacerein to create liquid SMEDDS, which was then heated in a water bath. Tween 80 and PEG 200 were added in a 3:1 ratio to this greasy mixture.	S-SMEDDS formulation s demonstrate d a >95% drug release in 20 minutes. It was reported that the %EE was 90%.	**Advantages-** The synthesized liquid SMEDDS's cloud point was greater than 80°C, indicating no chance of phase separation and the microemulsion would remain stable at physiological temperature. **Drawbacks-** The SEM analysis revealed liquid remnants, which might indicate that the	[57]

				microemulsion has not fully solidified.	
17.	**Sustained Release Matrix Tablets**	The tablets were prepared by the wet granulation method. In a tumbler mixer, all ingredients like HPMC, talc, and magnesium stearate (1:2) were mixed for 5 minutes and wetted with isopropyl alcohol.	From the *in vitro* drug release study, it was observed that at 12 hours, the percentage release was between 70 and 90 percent.	**Advantages-** From the plasma peak concentration, the time required to reach the peak was more which resulted in prolonged outcomes compared to free diacerein. **Drawbacks-** From *in vitro* study, an increase in HPMC concentration showed a decrease in diacerein release rates but this also resulted in aggregation of the different components in the formulation.	[58]

2B. Various types of dosage forms of Diacerein investigated by topical route of administration

The investigated topical drug delivery systems of diacerein provide many advantages such as being suitable for formulation into several topical solutions for easy application, including gels, creams, or patches. Topical formulations also minimize systemic exposure and any adverse effects by delivering tailored delivery specifically to the locations that are afflicted. Although many beneficial effects were reported, many side effects were also reported from the formulations restricted skin penetration, lower effectiveness, potential for allergic reactions or skin irritation, and varying rates of absorption because of the various types and states of skin [59].

For the preparation of emulgel, Carbopol 940 powder was dissolved in distilled water, and Tween 20 was dissolved with propylene glycol, methylparaben, and propylparaben, diacerein to create the emulsion. The cumulative drug release was found to be 98.89% which indicated that the emulgel based on Carbopol 940 provided a superior release. The pH of the formulation was observed to be in the range of (3.5-4), which is slightly acidic compared to the pH of the human skin. So, this can lead to skin irritations and problems when used topically [60].

The emulsion solvent diffusion method was used to create diacerein-based nanogel. Two independent variables, like the concentration of Carbopol 940 and eudragit, and three dependent variables—particle size, %EE, and % drug release at 24 hours, were used to improve the formulation using response surface methods. The %EE was found to be 82 ± 4.16% and the % drug release at 24 hours was found to be 90.13%. So, the formulation gives an almost immediate effect in the localized area of the body and reduces systemic exposure to the drug. The *ex vivo* study showed that the nanogels only penetrate a certain depth into the skin, which could compromise their therapeutic efficacy [61].

The transferosomes were formulated by thin film hydration to prepare the dual delivery loaded transferosomes, and the Box-Behnken design to optimize them. The formulation showed a remarkable %EE of 91.23±1.8% for diacerein and 89.50±1.5% for berberine HCl. Over 24 hours, the improved transferosomes released 82.09±0.81% of berberine HCl and 85.02±3.81% of diacerein, demonstrating a sustained drug release profile that is excellent for skin penetration. The diacerein and berberine HCl physical combinations lost

weight at temperatures close to 100 and above 200°C, due to functional groups' gradual removal [62].

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Table (2) provides the methods, advantages, and drawbacks of the studied dosage form based on diacerein, depending on the topical route of administration.

Sl. No	Formulations	Methodology	Outcomes	Advantages and Drawbacks	Ref.
1.	**Cream**	A two-phase technique was used to formulate the cream. At 90% of the melting point, the oil phase was moved into the heated aqueous phase. The fusing procedure was used to create the cream.	Diacerein was discovered to have a drug content of 98.54 % and *in vitro* drug release was 99.51%. The measured pH was 4.5. Yellowish color and semisolid structure were observed.	**Advantages-** From stability studies and drug release studies, it was confirmed that the formulation has a longer shelf life. **Drawbacks-** The absorption studies showed that the skin penetration of diacerein from the cream varies depending on the type of skin, so the effectiveness varies in each individual.	[63]
2.	**Liposomal Gel**	An aqueous dispersion of Carbopol 934 at 1% w/v was made and then with constant stirring, 2 mg of diacerein was added to an aqueous solution of 0.9% w/v tri-ethanolamine .	The %EE of liposomal formulations based on egg lecithin ranged from 57.92±1.02 % to 86.13± 1.19%. Using a pH 6.8 phosphate buffer, the system's maximal drug release (>90%) was accomplished in 16 hours.	**Advantages-** The *ex vivo* permeation study showed fold values indicating improved penetration of egg and soy lecithin-based liposomal gels over excised Wistar rat skin, which suggests satisfactory skin permeation of the formulation. **Drawbacks-** In the acute oral toxicity study, there was a minor fluctuation in levels of bilirubin, urea, creatinine, and other biochemical indicators as well as renal and liver function tests relative to the control group.	[64]

3.	**Microemulgel**	Castor oil was used to dissolve diacerein. The co-surfactant ethanol and surfactant Tween 80 were combined. The gelling agent Carbopol 934 was added to the micro-emulsion.	After 24 hours, the total *in vitro* drug release was 94.70%, which was twice as much as the control formulation. The %EE was found to be 98%.	**Advantage-** The zeta potential (ZP) measurements suggest that the formulations were stable and exhibited high particle size uniformity. These features imply that microemulgels would be appropriate, offering a regulated release of the active components. **Drawbacks-** The microemulgel was shown to have a high viscosity, which had an impact on drug release, a greater viscosity slowed down the rate of drug release.	[65]
4.	**Microsponge loaded Gels**	The quasi-emulsion solvent diffusion procedure was used to create diacerein-loaded microsponges using the polymers eudragit RS 100 and ethyl cellulose, which were subsequently added to gels.	The yield % was calculated after the microsponges were prepared. They were found to range from 70.12% to 86.52%. The results showed that the %EE ranged from 70.41 to 92.66%.	**Advantages-** The formulations were shown to have more drug dissemination after 12 hours, according to *in vitro* diffusion study. Consequently, gel formulation loaded with microsponge was improved to offer controlled drug release with all the required properties. **Drawbacks-** The viscosity of ethyl cellulose-containing microsponge formulation was found to be higher than the typical range.	[66]
5.	**Nanoemulgel**	The diacerein-based nanoemulgel was created using the ionic gelation process with natural anti-inflammatory	%EE was found to be 82 ± 4.16%. 95% of diacerein was released in 72 hours, according to *in vitro*	**Advantages-** The addition of chondroitin sulfate, chitosan, and argan oil, which have anti-inflammatory qualities, allowed Diacerein-nanoemulgel to maintain the medication's release	[67]

		, biodegradable polymers such as chondroitin sulfate and chitosan.	research using the Korsmeyer–Peppas model.	with excellent penetration and improved therapeutic capabilities. **Drawbacks-** Slight nanoparticle aggregation was observed in particle size distribution, which may lead to a disturbance in the therapeutic efficacy of the formulation.	
6.	**Nano-structured Lipid Carrier (NLC) Based Gel**	The lipid technique was performed to blend liquid and solid lipids that were heated to an identical temperature. Diacerein was added to the lipid phase. NLC was formed by cooling the hot oil-in-water pre-emulsion into an ice bath.	A diacerein-loaded NLC formulation that was optimized showed a 94.17% drug release over 24 hours and an %EE of 91.30%.	**Advantages-** The safety of the topical gel formulation on NLC was validated by a skin irritation test. *In vitro* study showed, NLC demonstrated a faster start and continuous functioning for up to 24 hours. **Drawbacks-** In an *ex vivo* study, very fast drug release was observed, which concludes that the effect of diacerein will last a comparatively short period when applied on the site of the skin.	[68]
7.	**Niosomal Gel**	Thin film hydration was used to create the diacerein-loaded niosomes, which were optimized by a 3-level Box-Behnken design. Span 60, cholesterol, and hydration time were chosen as independent variables.	The %EE was observed between 9.52% and 95.63%. A total drug release of 90.13% was found at 24 hours.	**Advantages-** Images of diacerein-loaded niosomes obtained by confocal laser scanning microscopy revealed that with less diacerein penetrating the dermis layer, niosomes showed a strong capacity to transport the drug into the viable epidermis layer. **Drawbacks-** The samples' particle sizes ranged from 306 nm to 650 nm, suggesting that niosomal size rose (P b 0.05) in a linear fashion	[69]

				as cholesterol content rose.	
8.	**Proniosomal Gel**	The coacervation process was used to manufacture proniosomes. Diacerein, including cholesterol, lecithin, and surfactant was placed in a wide-mouth container. Absolute alcohol was added to this.	The improved formulation's vesicle size, %EE, and drug release percentage were determined to be 5.5752, 96.8901%, and 95.3998%, respectively.	**Advantages-** The %EE is greatly impacted by variations in cholesterol. There was an increase in the observed %EE, notably when the cholesterol level was raised from 150 mg to 300 mg; however, the %EE was reduced when the cholesterol level was raised further. **Drawbacks-** Based on *in vitro* diffusion studies, which showed a fast drug release in the first phase. However, a slow release of diacerein from the proniosomal formulations was noted during the second phase.	[70]
9.	**Transferosomal Gel**	The reverse-phase evaporation technique was used to create the diacerein-loaded transferosome. Lipid, cholesterol, and surfactant were dissolved in a 2:1 v/v solution of chloroform and ethanol.	%EE of 91.23 ± 1.8 % were attained for diacerein and 89.50 ± 1.5 % for berberine HCl. The *in vitro* drug release was found to be 85% in 24 hours.	**Advantages-** According to the investigations, the medication penetrates the skin. To increase the efficacy of treatment, the pathological state and target skin receptors were preferred above topical gel administration. **Drawbacks-** According to the response plot, medication release rose when lipid and surfactant levels rose while increasing cholesterol levels caused drug release to fall.	[71]

2C. Various types of dosage forms of Diacerein investigated by parenteral route of administration

Injections and other parenteral formulations offer direct systemic circulation distribution, guaranteeing a quicker start of action and greater absorption. Patients who need quick relief from severe osteoarthritis or who are unable to take oral drugs because of swallowing issues or gastrointestinal

upset would benefit most from this approach. To create stable and efficient parenteral formulations of diacerein, issues such as injection site irritation, stability, and solubility must be addressed [72].

Table (3) provides the methods, advantages, and drawbacks of the studied dosage form based on diacerein, depending on the parenteral route of administration.

Sl. No	Formulations	Methodology	Outcomes	Advantages and Drawbacks	Ref.
1.	**Hyaluosomes**	Soy lecithin and Tween 80 as an edge activator in a molar ratio of 85:15 with diacerein were used to generate diacerein-loaded hyaluosomes utilizing the thin film hydration process.	Hyaluosomes were able to attain a high %EE of 90.7%. Over 48 hours, the optimized formulation released less than 50% drug, while the aqueous diacerein dispersion released more than 50% drug in the first 4 hours.	**Advantages-** After intra-articular injection, the produced diacerein-loaded hyaluosomes' capacity to enhance the *in vivo* inflammatory state and cartilage degradation in rats was evaluated, and the results showed better function in preventing inflammation and cartilage damage. **Drawbacks-** *In vitro* drug release revealed that whereas the water diacerein dispersion released more than 50% of its contents in the first 4 hours, the optimized diacerein-loaded hyaluosomes released less than 50% of it over 48 hours.	[73]
2.	**In-situ Gel**	Diacerein in-situ gels were prepared using the standard "cold method." Poloxamer-407, and copolymer Carbopol 394 were added and distributed. After being dissolved in DMSO and ethanol, the	The *in vitro* drug release investigation showed controlled releases of 39.19% and 38.97% at 24 hours, respectively. %EE of 95.30% was observed.	**Advantages-** The in-situ gel of diacerein stayed stable, responded to temperature changes, and gelled at body temperature. Diacerein's regulated release from the tailored in-situ gel improved the therapeutic approach. **Drawbacks-** The viscosity study revealed that too	[74]

		drug was added, and the final concentration was adjusted using cold water.		much viscosity can make the gel difficult to spread uniformly, while too little fluidity might make it stick poorly to the skin. So, it was challenging to get the gel to the ideal viscosity for spreading and easy application on the skin without sacrificing structural integrity.	
2.	**Surface Modified Iron Oxide Magnetic Microparticles (SMIOMPs)**	The co-precipitation method was used to create iron oxide particles using solutions of ferric sulfate and ferric chloride. Then, using a neodymium magnet, the produced iron oxide particles (IOMPs) were gathered and, chitosan and diacerein were added to create the SMIOMPs.	The improved formulation produced an 85.25% drug %EE. The aqueous diacerein dispersion and diacerein-loaded IOMPs released around 50% of the drug in the first 4 hours, but the optimized diacerein-SMIOMPs released less than 50% of the drug over 48 hours.	**Advantages-** Subsequent *in vivo* research demonstrated that the optimized formulation reduced the rats' knee edema. **Drawbacks-** Variables' effects on ZP revealed a significant interaction between the surface modifier type and the molar concentration of FeCL3 on the synthesized diacerein-loaded SMIOMPs' absolute ZP values.	[75]

2D. Various types of dosage forms of Diacerein investigated by transdermal route of administration

To increase diacerein's skin permeability, transdermal formulations include penetration enhancers or carriers based on nanotechnology, such as liposomes and nanoparticles. A regulated and prolonged release of diacerein is provided by transdermal administration, which reduces the frequency of doses and guarantees steady therapeutic levels throughout time. Since it lowers the chance of drug interactions, this approach is especially helpful for individuals with gastrointestinal issues or those taking many medications [76].

Table (4) provides the methods, advantages, and drawbacks of the studied dosage form based on diacerein, depending on the transdermal route of administration.

Sl. No	Formulations	Methodology	Outcomes	Advantages and Drawbacks	Ref.
1.	**Elastosomes**	Film hydration was used to create the elastosomes. Sodium taurocholate, cholesterol, and Span 60 were combined. A combination of methanol and chloroform was added. Then, ultra-pure distilled water was used to hydrate the dry film.	The range for the proportion of diacerein trapped in the elastosomes was 96.25 ± 2.19%. For over 8 hours, the *in vitro* drug release study showed about 75% drug release.	**Advantages-** The optimized formulation's safety and non-irritability when applied to rats' skin were confirmed by the *in-vivo* histological investigation. **Drawbacks-** Variability in the deformability index, which is essential for skin penetration, suggested possible irregularities in vesicle flexibility.	[77]
2.	**Novasomes**	The formulation was prepared using the thin film hydration process. Drug, Span 60, cholesterol, and stearic acid were mixed in a chloroform-methanol combination and then sonicated for 10 minutes.	The optimized formulation had a polydispersity index of 0.309±0.016, a vesicle size of 275.2±2.68 nm, and an %EE of 69.415±0.234 percent.	**Advantages-** The compatibility was verified by the FTIR research, and the high ZP suggests improved physical stability and a low likelihood of aggregation. Therefore, to prevent oral adverse effects, diacerein-loaded novasomal dispersion might be created as a platform for transdermal drug administration. **Drawbacks-** To optimize the %EE using vesicles, the ratio of cholesterol to non-ionic surfactant needed to be properly balanced, since the %EE study showed low cholesterol content leads to inadequate entrapment, which promotes drug leakage and vesicle fusion.	[78]

3.	**Self-Dissolving Microneedles**	Solid dispersion of diacerein utilizing PEG 4000 by fusion technique was performed. HPMC and PVP, with PEG 400 were selected as co-solvent.	The addition of PEG 400 increased diacerein loading in microneedles to 390.35 ± 4.28 µg per array. Improved drug permeation was observed at 74.39% and skin deposition at 15.75% after 24 hours.	**Advantages-** In the rat paw edema model, microneedle-assisted diacerein gel had a favorable anti-inflammatory effect and decreased diarrheal episodes. When evaluated under accelerated stability circumstances, the gel displayed the required properties at 5°C±2°C. **Drawbacks-** Diacerein was still present in the baseplate in 12% of cases. As a result, a CMC-based gel with a 0.4% solid dispersion of diacerein (3% w/v) was customized.	[79]

3. Necessity of creating novel Diacerein-based delivery methods to treat RA

Future research on diacerein delivery systems for RA should focus on improving their stability and bioavailability [80], ensuring the drug remains effective and reaches its target within the joint [81]. Researchers also need to enhance targeting capabilities [82], minimizing off-target effects and improving drug concentration at the site of inflammation [83]. Evaluating the potential of these systems to not only manage symptoms but also delay or halt the progression of RA is crucial [84]. This may involve investigating the combination of diacerein with other therapeutic agents for a synergistic effect [85]. Developing novel drug delivery technologies, such as stimulus-responsive systems that release diacerein in response to inflammation markers, could further enhance treatment precision and efficacy [86]. To enhance the efficacy of diacerein in treating arthritis, future research should focus on targeted drug delivery systems and combination therapies [87]. Developing innovative delivery methods, such as intra-articular injections with biocompatible nanoparticles or hydrogels, can concentrate the drug directly at the site of inflammation within the joint [88,89]. This targeted approach may improve diacerein's therapeutic index by maximizing its impact on affected tissues while minimizing systemic exposure and potential side effects [90]. Additionally, exploring diacerein's use in combination therapies, potentially with existing drugs targeting different pathways in arthritis pathogenesis, could provide synergistic benefits and improve overall treatment outcomes [91]. By leveraging advancements in drug delivery systems, the treatment of RA with diacerein may significantly improve, leading to better patient outcomes and a reduced burden on healthcare systems.

4. Future prospects for the development of various Diacerein-based innovative formulations for excelling treatment of RA

Diacerein, despite its therapeutic promise in RA management, faces limitations due to its poor solubility and associated side effects. This necessitates exploring innovative formulations that enhance its delivery and therapeutic efficacy which are highlighted in Table 5.

Table (5): Presumption of concept and potential of Diacerein-based formulations for treatment of RA.

Innovative Diacerein Formulations	Concept	Potentiality	Future Prospects	Ref.
Targeted Nano-particles: Precision Medicine for Joints	En-capsulating diacerein within nano-sized carriers like liposomes, polymeric nano-particles, or nanocrystals.	1.Significantly improves diacerein's solubility and bioavailability. 2. Enable targeted delivery to inflamed joints, concentrating the drug at the site of action. 3. Minimize off-target effects and reduce systemic toxicity.	1.Surface modification of nanoparticles with ligands that bind specifically to cartilage cells for active targeting. 2. Development of stimuli-responsive nanoparticles that release diacerein in response to specific physiological cues, such as changes in pH or enzyme activity, within the joint.	[92]
Sustained-Release Implants: Long-Term Relief, Minimal Intervention	Developing biodegradable implants loaded with diacerein, designed for injection or insertion near affected joints.	1. Provide sustained drug release over extended periods, potentially weeks or months. 2.Significantly reduces the dosing frequency, improving patient compliance as well as convenience. 3.Maintain consistent therapeutic levels of diacerein in the joint, maximizing its therapeutic effect.	1.Designing implants with adjustable release rates to personalize treatment based on disease severity and patient response. 2.Incorporating growth factors or chondroprotective agents within the implant to promote cartilage renewal alongside symptoms relief.	[93]
Transdermal Delivery Systems: Bypassing the Gut, Enhancing Comfort	Utilizing patches, micro-needles, or specialized gels to deliver diacerein through the skin, directly to	1. Avoid first-pass metabolism in the liver, potentially increasing the bioavailability and reducing the required dose. 2.Reduce gastrointestinal side effects, a common	1. Incorporation of chemical enhancers or physical methods (e.g., iontophoresis) to improve the skin permeability for diacerein. 2.Developing discreet and comfortable patches that are easy to	[94]

	the bloodstream or underlying joint tissues.	drawback of oral diacerein. 3. Offer a non-invasive and advantageous replacement to injections, which improves patient acceptance.	apply and withdraw, enhances patient adherence.	
Advanced Hydrogels: Responsive Delivery, Enhanced Residence Time	Engineering chitosan hydrogels with stimuli-responsive polymers that respond to specific triggers within the joint.	1. Achieve on-demand drug release, triggered by physiological cues like changes in temperature or pH associated with inflammation. 2.Personalize treatment by tailoring drug release profiles to individual patient needs. 3. Improve drug retention time at the site of action, enhancing therapeutic efficacy.	1.Developing injectable, self-healing hydrogels for minimally invasive delivery and improved residence time within the joint. 2.Incorporating imaging agents within the hydrogel to monitor drug release and treatment progress.	[95]
Combination Delivery: Multi-Target Approach for Enhanced Efficacy	Co-enclosing diacerein with other therapeutic agents, such as hyaluronic acid or chondroitin sulfate, within a single delivery system.	1.Achieve synergistic effects by targeting multiple pathways involved in OA pathogenesis. 2.Provide comprehensive symptom relief and potentially slow down disease progression. 3. Simplify treatment regimens for patients by combining multiple therapies	1. Identifying optimal drug combinations and ratios for maximizing therapeutic efficacy and minimizing side effects. 2. Development of personalized combination therapies tailored to individual patient needs and disease stages.	[96]

		into a single formulation.		

These innovative formulations hold immense potential to revolutionize diacerein therapy, offering patients with RA new avenues for effective, safe, and convenient treatment options.

3. Conclusion

In conclusion, enhancing diacerein administration methods presents a workable approach to increasing the medication's efficacy in the management of RA. The study highlights several innovative formulations that reduce side effects while resolving diacerein's solubility and bioavailability issues. Topical gels, controlled-release pills, and sophisticated nanocarriers are some of these formulations. The advantages of various systems vary; better patient compliance and targeted delivery are among them. The application of cutting-edge technologies such as hydrogel-based systems and combination deliveries in customized medicine may improve the therapeutic efficacy of diacerein. Continued research and clinical trials are necessary for sustained release, mitigating treatment effects, and enhancing these delivery methods. The ultimate objectives of these advancements are to improve patient care to make diacerein a more convenient and appealing option for the treatment of RA.

Abbreviations

OA, Osteoarthritis; RA, Rheumatoid Arthritis; IL, Interleukin-1; TNF-α, Tumor necrosis factor-alpha; MMPs, Matrix Metalloproteinases; TGF, Transforming Growth Factor; BCS, Biopharmaceutics Classification System; HPMC, Hydroxypropylmethylcellulose; CMC, Carboxymethyl Cellulose; %EE Encapsulation Efficiency; SLNs, Solid Lipid Nanoparticles; ISO, Isonicotinamide; NIC, Nicotinamide THE, Theophylline; XRD, X-ray Diffraction; PEG, Polyethyleneglycol; SDs, Solid Dispersions; DSC, Differential Scanning Calorimetry PXRD, Powder X-ray diffractograms; SEM, Scanning Electron Microscopy; LPs, Liposomes; SST-DNL, Somatostatin Analogue; FTIR, Fourier Transfer Infrared Spectroscopy; PLLA, Poly L-lactic acid; ODFs, Oral Dissolving Films; ODTs, Oral Disintegrating Tablets; PVP K30, Polyvinylpyrrolidone; PLs, Proliposomes; DMSO, Dimethyl sulfoxide; S-SMEDDS, Solid Self-Microemulsifying Drug Delivery System; ZP, Zeta Potential; NLCs, Nanostructured Lipid Carriers; SMIOMPs, Surface Modified Iron Oxide Magnetic Microparticles; IOMPs, Iron Oxide Particles.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The above data are collected from PubMed, PubChem, Drug Bank, Scopus database.

Authors Contribution

Subarnarekha Maitra, Dibya Sinha, and Maitreyee Mukherjee: Literature review, writing and editing the draft, figures, and table drawing. Sreemoy Kanti Das, Leena Kumari, and Tathagata Roy: Conceptualization, supervision, proofreading, and administration.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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