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Research Article

Formulation and *In Vitro* Evaluation of Diacerein Microspheres Using Ethyl-cellulose as Rate Retarding Agent

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Abstract

Diacerein (DCN) is a newly developed anti-inflammatory drug that is chemically and pharmacologically different from non-steroidal anti-inflammatory drugs (NSAIDs). Diacerein is poorly soluble in water and possesses a slower dissolution rate. Diacerein microspheres development significantly improved not only the aqueous solubility but also the drug dissolution rate. Similarly, Diacerein microspheres enabled us to control the release rate of the drug, leading to minimized dosing frequency. Using the solvent evaporation method, diacerein microspheres were prepared with ethyl cellulose and hydroxyl propyl cellulose as encapsulation material. In this study, six different formulations were prepared using different proportions of ethyl cellulose, and two other formulations with different combinations of ethyl cellulose and hydroxyl propyl cellulose were also prepared. Additionally, different proportions of gelatin were used as emulsifying agents. The formulated microspheres were evaluated through Fourier Transform Infra-Red Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), percentage yield, chemical assay, release kinetics, in vitro dissolution studies, and entrapment efficiency. Afterward, FTIR spectra ensured that there was no drug-to-polymer interaction. Moreover, SEM confirmed the spherical nature of microspheres and that the drug entrapment efficiency was 89%. Our study demonstrates that microspheres could be a suitable technique to formulate a sustained release formulation of DCN.

Keywords: Sustained release, drug delivery, diacerein, microspheres

1. Introduction

Osteoarthritis (OA) is a routine life joint disorder that mostly affects the hands, knees, and spine. Particularly, the synovial joints are highly prone to this disease. OA manifests in the form of morning stiffness of joints, restricted body movements, and severe joint pain which subsides upon resting. Notably, OA is rarely seen before age 40. The phenomenon of joint swelling is due to the formation of osteophytes (Altman 1991). Initially, OA is often dismissed as a typical muscular ache, stiffness, and body pain, as a normal sign of aging. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for symptomatic relief from pain; however, the use of NSAIDs is associated with gastrointestinal and vascular side effects (Zhang et al. 2008) This prompted researchers to explore other treatment options, which led to the discovery of Diacerein (DCN).

Unlike NSAIDs, DCN, an IL-1 inhibitor, does not interfere with prostaglandin synthesis (Spencer and Wilde 1997). However, diarrhea, skin rashes, and discoloration of urine are among the common side effects of DCN (Pelletier et al. 2000). DCN is beneficial for people who are at higher risk of gastric bleeding. Since DCN has a shorter half-life

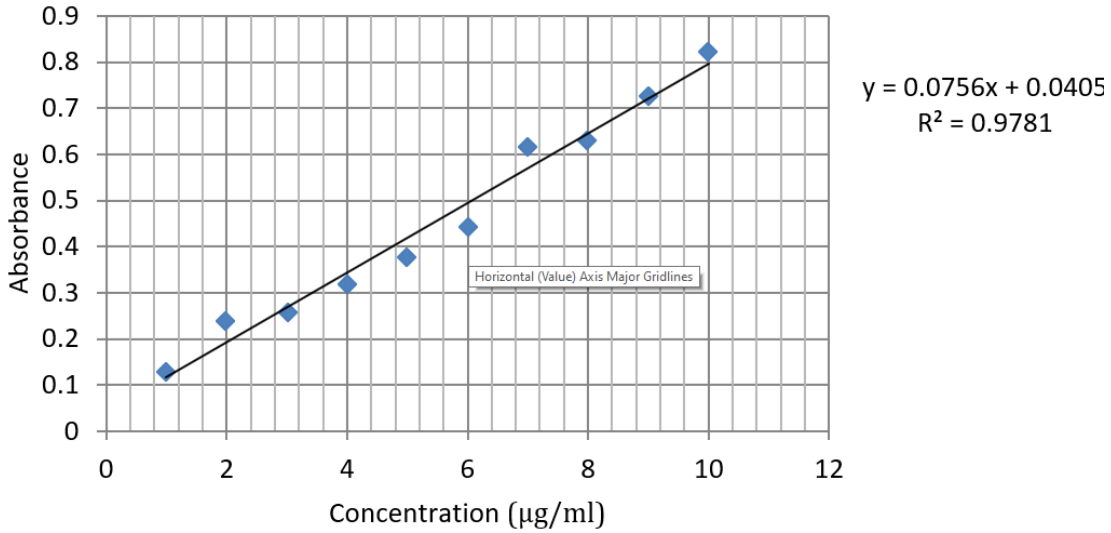

Figure 1. The figure shows the calibration curve of Diacerein in buffer 6.8.

Table 1. The table below depicts the concentration VS absorbance values of the sample.

Concentration (ug/mL)	Absorbance
1	0.1285
2	0.2401
3	0.217
4	0.3196
5	0.3770
6	0.4418
7	0.6154
8	0.6310
9	0.7275
10	0.8221

of 4.3 hours, it requires a higher dosing frequency, resulting in patient non-compliance, which is common for drugs with short half-life. Moreover, maintaining a therapeutic plasma concentration of such drugs for a longer period remains a challenge. This limitation led to the discovery of new drug delivery systems that can maintain the required plasma concentration of those drugs over a longer period.

Microencapsulation is a method in which tiny drug particles are enclosed in a continuous polymer phase through the coating. This process yields particles with a diameter range of 300-800 nm called microspheres (Agnihotri et al. 2012). The microspheres are more stable and ensure prolonged as well as controlled drug delivery, resulting in reduced dosing frequency, minimum adverse effects, and enhanced patient compliance (Nagpal et al. 2012). Furthermore, microspheres can be prepared by solvent diffusion, spray drying, polymerization, coacervation, and spray congealing; however, solvent evaporation is the most frequently used method (Tiwari, Verma, and Batra 2011).

Cellulose-derivative polymers have often been used for drug delivery systems. Ethylcellulose (EC) is an inert, stable, non-toxic, and easily compressible polymer with several

Table 2. The table below shows the composition of different formulations.

Formulation	Drug (mg)	EC (mg)	HPC (mg)	Gelatin (%)
E1	100	1000	-	0.5
E2	100	700	-	0.5
E3	100	500	-	0.5
E4	100	1000	-	1
E5	100	700	-	1
E6	100	500	-	1
A1	100	800	100	0.5
A2	100	700	200	0.5

Table 3. This table shows the recovery of microspheres.

Formulations	Mean Input(mg)	Mean Output	% Recovery
F1	1100	896	81.454
F2	800	480	60.500
F3	600	378	63.000
F4	1100	960	87.000
F5	800	633	79.000
F6	600	426	71.00
A1	900	832	92.000
A2	900	720	80.000

Table 4. Hydration rate of microspheres is depicted in the following table.

Formulations	Mean Weight	Mean weight of dry microspheres	Mean Hydration
F1	1239	960	129.06
F2	729	480	152.021
F3	766	426	179.89
F4	1155	895	129.06
F5	701	633	110.82
F6	448	378	118.69
A1	921	832	110.78
A2	890	720	123.71

pharmaceutical applications, such as binder, film, and matrix-forming agents. Previously the effect of EC, hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), and several other polymers have been investigated. The investigation revealed that EC possessed good capability of retarding the drug release rate from matrices tablets (Akhlaq et al. 2014, Jan et al. 2011, Jan, Khan, and Hussain 2012, Jan et al. 2013, Syed et al. 2013, Shah et al. 2011, Shah et al. 2012, Shah and Khan 2012).

The objective of this study was to prepare and characterize DCN microspheres, investigate their in vitro release behavior, and develop a prospective, cost-effective, once-a-day formulation of the drug for improved patient compliance and treatment outcomes.

2. Materials and Methods

DCN was gifted by Consolidated Chemical Laboratories (Pvt.) Ltd Lahore Pakistan. EC and HPMC were purchased from BDH Fluka Riedel, and Sigma Aldrich, respectively. Additionally, analytical grade solvents were used in the study.

2.1. Standard Calibration Curve

A standard stock solution of DCN 1mg/ml was prepared. After the filtration, various dilutions of DCN in phosphate buffer of pH 6.8 were carefully made, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 µg /ml. The absorbance and calibration curve were measured by plotting absorbance on the Y-axis and concentrations on the X-axis. Table 1 shows the concentrations and relevant absorbance. The calibration curve is shown in Figure 1.

2.2. Microspheres Preparation

Microspheres were prepared by using the classical solvent emulsion evaporation method. A fixed amount (1000mg, 700mg, 500 mg) of polymer (EC, EC: hydroxyl propyl cellulose (HPC)) and DCN (100mg) were dissolved in 20 ml of dichloro methylene (DCM). The composition of all formulations is described in Table 2. The prepared clear organic solution was added at room temperature, under continuous mechanical stirring (1100 rpm), to 100 ml of 0.5% (w/v) gelatin aqueous solution. Agitation was then continued until the complete evaporation of DCM. The microspheres were then collected in a filter paper. After filtration, microspheres were washed using distilled water and kept overnight to dry.

2.3. Physicochemical Characterization of Microspheres

2.3.1 Recovery of Microspheres

The % age yield of the microspheres was calculated using the following formula

$$\% \text{ yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer used}}$$

2.3.2 Microsphere Hydration

After filtration, the microspheres produced were weighed immediately (M1) and compared with the weight of dried microspheres to determine the hydration rate. The percentage of microsphere hydration was calculated using the following equation:

$$\text{Microsphere Hydration (\%)} = \frac{M_1}{M_2} \times 100$$

2.3.3 Drug Loading Capacity

The drug loading efficiency was determined as a percentage of drug loading according to the following equation:

Drug Loading = Mass of drug in microspheres/Mass of microspheres × 100

2.3.4 Drug Entrapment Efficiency

Microspheres (25 mg) of DCN were crushed and dissolved in 50 ml phosphate buffer pH 7.4 for 24 hours. After filtration with Whatmann filter paper no. 41, the filtrate was further diluted appropriately and analyzed for drug content using a UV-visible spectrophotometer at 257 nm. The drug entrapment efficiency was determined with the help of a formula:

% Drug entrapment efficiency = (Practical Drug content / Theoretical Drug content) X100

2.4 Rheological Properties of Prepared Microspheres

2.4.1 Bulk and Tapped Density

1g of microsphere from each formulation was sieved through 18 # mesh, and then placed in a 10mL measuring cylinder; afterward, the volume occupied was measured.

To calculate loose bulk density, the following equation was used:

$$Bulk\ Density = \frac{M}{V_0}$$

Where,

M =Weight of microsphere

V_o =Volume occupied

A typical tapping method was applied to determine the tapped density of microspheres. After introducing the weighed microspheres into a measuring cylinder, we tapped it 100 times until no volume change was observed. Tapped density was calculated using the equation:

$$Tapped\ Density = \frac{M}{V_f}$$

Where,

M = Initial weight of microspheres

Table 5. The following table shows encapsulation efficiency of microspheres.

Formulations	Theoretical drug loading (mg)	Actual Drug Loading	% Drug Loading
F1	100.0	62.84	62.84
F2	100.0	53.87	53.87
F3	100.0	64.45	64.45
F4	100.0	81.81	81.81
F5	100.0	59.99	59.99
F6	100.0	76.98	76.98
A1	100.0	64.42	64.42
A2	100.0	75.89	75.89

V_f = Final tapped volume in ml

2.4.2 Compressibility Index (CI)

It is an indirect method to measure rheological properties such as size, bulk density, moisture contents, surface area, and cohesion among materials. It is also called Carr's index (USP, 2007). Carr's index was calculated by using the following equation:

$$Carr'Index = \frac{(Tapped\ Density - Bulk\ Density)}{tapped\ Density} \times 100$$

2.4.3 The Angle of Repose

The maximum angle between the surface of the pile of microsphere and the horizontal plane is called the angle of repose. To calculate the angle of repose, microspheres were passed through a funnel, resulting in a heap of microspheres. Following the heap formation, the height of the heap and radius were calculated.

$$tan\theta = \frac{h}{r}$$

Where,

h = Height of heap formed

r = Radius of cone base

2.4.4 Hausner's Ratio

This ratio depicts the flowability characteristics of microspheres. Hausner's ratio <1.2 is considered good for free flow.

For calculating Hausner's ratio, the equation used is,

$Hausner's\ ratio = Volume\ before\ tapping\ /\ Volume\ after\ tapping$

2.4.5 Fourier Transform Infra-Red Spectroscopy (FTIR)

The drug-polymer compatibility was studied through FTIR spectroscopy (FTIR Shimadzu 8,400 S). The FTIR spectra were recorded for pure drugs, polymers, and a mixture of drugs and polymers. The KBr disc method was used to prepare samples in KBr disks (2 mg samples in 200mg KBr). These samples were scanned in the 4000 to 400 cm-1 frequency range to obtain resolution at 2 cm^{-}.

2.4.6 Scanning Electron Microscopy (SEM)

SEM technique was employed to characterize the shape and surface morphology of microspheres.

2.4.7 Particle Size Analysis

Determining particle size is important as it will help assess the surface area available for drug release.

2.5 *In Vitro* Drug Release

The drug release studies of DCN microspheres were conducted using USP dissolution apparatus 2(rotating paddle method). Freshly prepared 900 ml phosphate buffers of pH 6.8 and pH 7.4 were used as buffer medium, with temperature set at 37°C±0.1°C, and speed of paddles at 100 rpm. An aliquot of release medium (5 ml) was withdrawn at specified time intervals and was replaced with an equal amount of freshly prepared buffer. The samples collected were filtered and analyzed using a UV-VIS spectrophotometer to determine the contents of DCN at 257 nm. The concentration of DCN was calculated using the standard calibration curve.

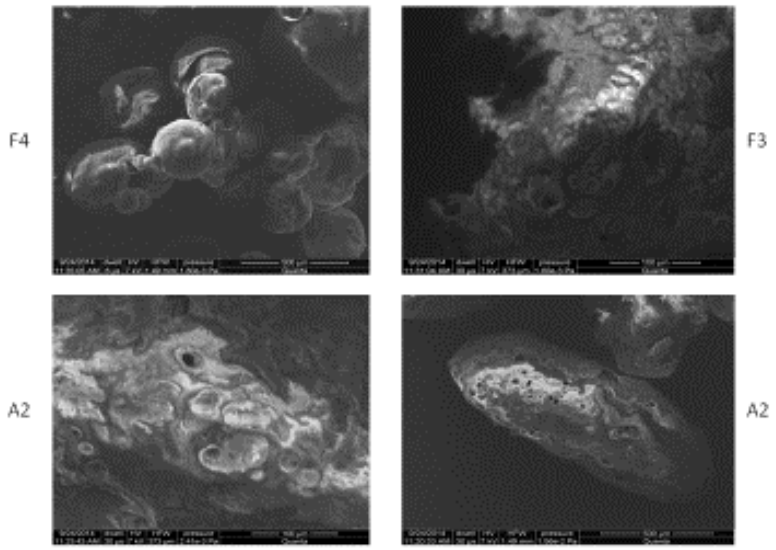

Figure 2. The above figure shows SEM results of selected microspheres.

2.6 Drug Release Kinetics:

A model-dependent approach was used to investigate the drug release mechanism of the microspheres. The Korsmeyer-Peppas equation is commonly used to describe drug release from various pharmaceutical formulations, particularly when it comes to controlled release systems. The equation is often written as:

$$\frac{Q_t}{Q_\infty} = K_n tn$$

Where:

- Qt is the amount of drug released at time t,
- $Q\infty$ is the total amount of drug released at infinite time,
- K is a constant,
- n is the diffusional exponent, dictating the drug transport mechanism.

The interpretation of the diffusional exponent (n) is as follows:

- If n= 0.5, the drug follows a quasi-Fickian diffusion pattern.
- If n > 0.5, anomalous or non-fickian mechanism of drug release and transportation of drug occurs by swelling and diffusion-controlled release.
- When n=1, non fickian, zero-order Case-II transport release is followed. (Mechanism Swelling controlled mechanism).

3 Results and Discussions

3.1 Recovery of Microspheres

The concentration of gelatin largely affects the weight of microspheres formed. Recovery is the weight percentage of the total weight of raw material. The recovery of microspheres is improved by adding gelatin in microcapsule formation (Lai and Tsiang 2004). When used in high concentrations, gelatin significantly decreases the chances of irregularly shaped microsphere yield, as it prevents agglomeration and results in high microsphere formation. When HPC is added, its hydrophilic nature hinders the formation of microspheres, leading to aggregation and the contents of microspheres being lost in an aqueous continuous phase (Sajid and Akash 2013). The percentage recovery is shown in Table 3.

3.2 Hydration Rate of Microspheres

The degree of hydration of microspheres is affected by factors like solvent miscibility, and solubility of water polymers. In the current study, methylene chloride (solvent) is insoluble

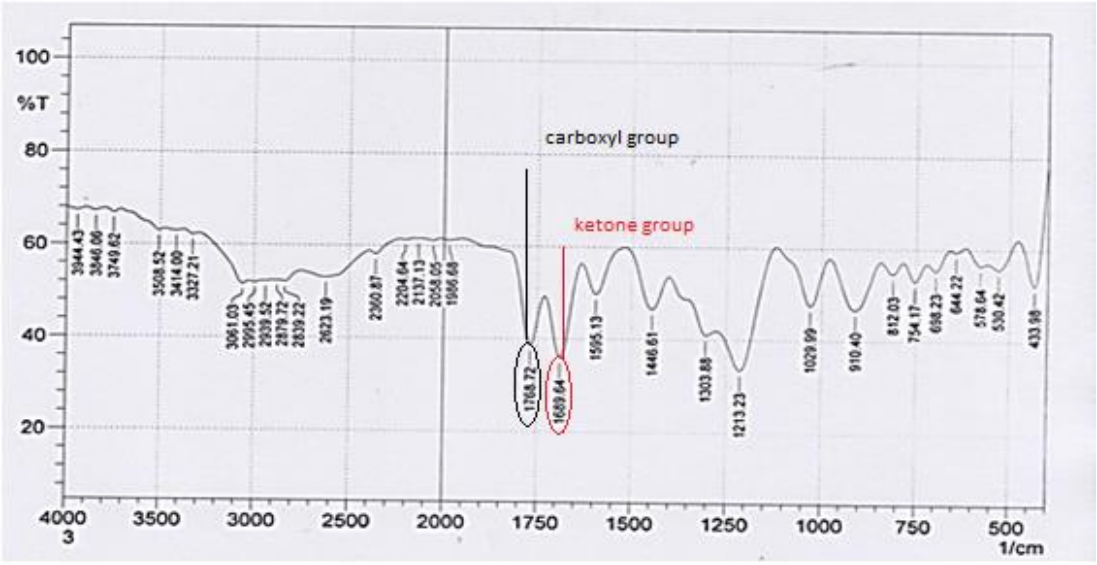

Figure 3. The above figure depicts FTIR spectra showing pure drug (Diacerein).

in water, EC (polymer), is hydrophobic, while HPC is naturally hydrophilic. During solvent evaporation, methylene chloride evaporates, leaving behind compact monolithic matrix-type microspheres. Due to the hydrophobic nature of EC, it does not allow water to penetrate microspheres; therefore, increasing the concentration of EC decreases the hydration rate. While the hydrophilicity of HPC allows the entry of water to a small extent. Thus, the formulations A1 and A2, which have both EC and HPC, are hydrated and are aggregated a bit (Sajid and Akash 2013). The hydration rate of all formulations is presented in Table 4.

3.3 Encapsulation Efficiency of Microspheres

The microspheres with higher concentrations of EC showed better encapsulation efficiency as the polymer weight viscosity of the disperse phase increased, resulting in an increased microsphere size (André-Abrant, Taverdet, and Jay 2001). This leads to an increase in drug encapsulation efficiency. The microspheres produced were smooth-surfaced, and the release of the drug was delayed. Using a higher molecular weight polymer, like EC, enhanced the entrapment efficiency. The use of methylene chloride is justified as it yields higher encapsulation efficiency than chloroform (Bodmeier and McGinity 1988). The increased concentration of HPC increased entrapment efficiency. The encapsulation efficiency was increased when a higher concentration of gelatin was used (Jyothi et al. 2010). The encapsulation efficiency of the formulations is depicted in Table 5.

3.4 Rheological Studies of Microspheres

The flow properties of microspheres depend upon the emulsifying agent, gelatin, and the polymer used. From the data obtained, we can assess that EC increased the surface smoothness, and subsequently, the flow properties (Murtaza 2012). However, a decrease in HPC concentration improved its flow characteristics.

Rheological data of all eight formulations is expressed in terms of bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. The compressibility index of all formulations was below 15 %, indicating excellent flow properties. The Hausner's ratio was below 1.15, demonstrating the free-flowing nature of all formulations of prepared microspheres. Similarly, the angle of repose for all six microsphere formulations was below 30^{o}, an

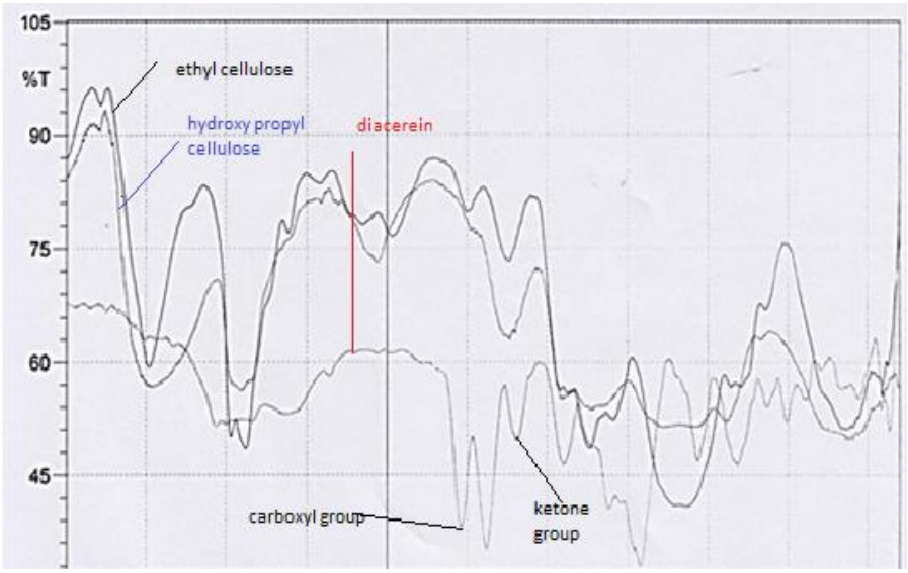

Figure 4. This figure shows FTIR spectra of microspheres having drug, EC and HPC.

indication of the free-flowing nature of the microspheres (Rekhi and Jambhekar 1995).

3.5 Scanning Electron Microscope (SEM)

SEM images demonstrated that all the formulations had spherical morphology. Notably, formulations developed using 1 % gelatin depicted smoother surfaces than formulations with 0.5 % gelatin. The formulation prepared with a combination of EC and hydrophilic HPC had a relatively less smooth surface (Lai and Tsiang 2004). Similar results were discussed by Lai and Tsiang et al. in 2004, who encapsulated acetaminophen using poly (L-latide) gelatin or polyvinyl alcohol as prospective colloids, which indicates that the use of gelatin imparts smoothness to the microsphere surface.

3.6 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy of DCN and DCN microspheres was conducted to observe drug excipients compatibility. DCN has a ketone and carboxylic groups at 1689 cm^{-1} and 1768 cm^{-1}, respectively. The hydroxyl group was observed in the 3327 cm^{-1} to 3508 cm^{-1} range at a frequency of 3346 $cm^{-1,}$ depicting the C-H deformations. Moreover, stretching was evident in the range of 3061 cm^{-1} to 2839 cm^{-1} (Stevens and Krieger 1991). Similarly, the IR spectra of other excipients were also analyzed to rule out any significant interaction between the active drug and polymers used. This became clear by looking at individual FTIR spectra showed no drug-polymer or polymer-polymer interaction (Dhanashri Subhash Yadav 2012).

3.7 Particle Size Analysis

The particle size of selected formulations was calculated by using a particle size analyzer (Horiba, LA-920). The particle size of all formulations was in the size range of 300-400 micrometers.

3.8. *In Vitro* Drug Release

DCN microspheres phosphate buffer with pH 6.8 was used to conduct dissolution studies. Drug polymer ratio manifested its effects on the drug release profile. The drug release happened in two phases, initially a burst release, followed by a sustained release pattern. The burst release could be due to the concentration of drug embedded on the microsphere's surface where microspheres swell and erosion of the drug core occurs and equilibrium is attained. Figure 1 shows the DCN microspheres drug release for all prepared batches. Formulations F1 and F3, with higher polymer concentrations, have poor drug release

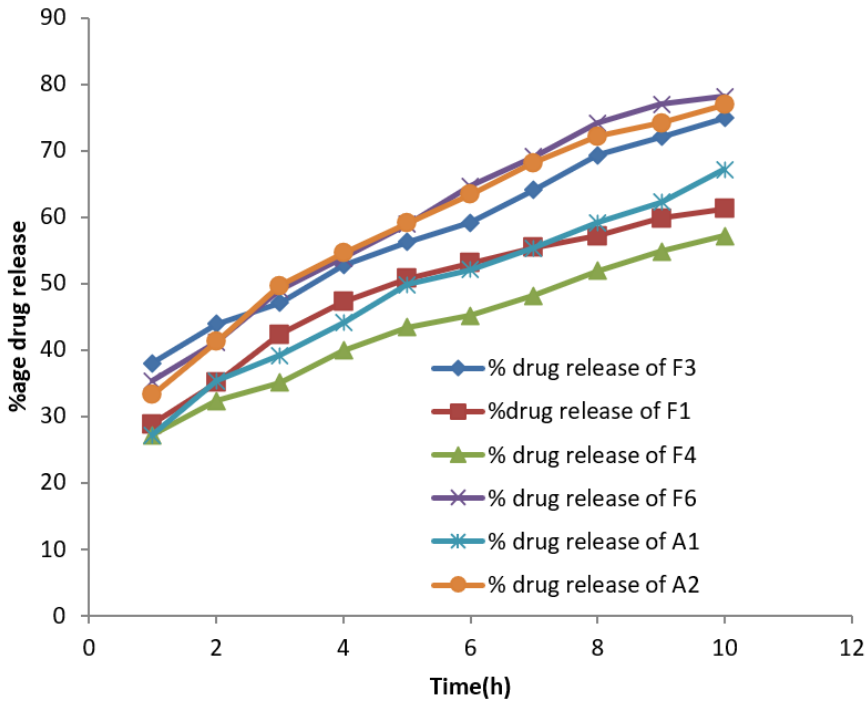

Figure 5. The above figure shows % diacerein *in vitro* release of all formulations.

compared to F3 and F6, which have lesser amounts of polymer. A1 and A2 have EC combined with HPC; when their ratio is low, better release is observed. A higher amount of gelatin produces better-sustained action with a more compact matrix and hard microspheres. A lower concentration of gelatin generates microspheres of the porous structure.

The results revealed that all the microspheres followed Korsemeyer-Peppas release kinetics due to their regression (R^2) value near 0.999. Values of n from the Korsemeyer-Peppas model were observed to be less than 0.5, showing non-fickian diffusion controls of microspheres**.**

4. Conclusion

From the results, it is clear that encapsulation of DCN has been accomplished by using EC polymer, using the W/O solvent evaporation method. Furthermore, various characterization methods, e.g. DSC, FTIR, and SEM, confirmed the microsphere formation. The effects of different variables were assessed, such as the concentration of polymer and the emulsifying agent used. All microspheres developed were free-flowing. FTIR results showed that the experimental parameters resulted in a uniform distribution of the drug matrix, without any significant interaction between the drug and the polymers. So, EC can be used for microencapsulation purposes. Notably, the combination of EC and HPC increased the recovery and encapsulation efficacy of microspheres. However, EC microspheres produced better results. Gelatin showed better encapsulation efficiency when used in higher concentrations. The formulation (F4) showed the best results for every parameter, exhibiting the balance between gelatin and polymer concentrations. All formulations followed Korsemeyer-Peppas release kinetics and the value of n was found to be less than 0.5, indicating non-fickian release kinetics. Further studies regarding *in vivo* parameters could be evaluated to assess the biocompatibility and release behavior inside the physiological environment so that it could be produced at a commercial scale.

Conflict of Interest
The authors declare that they have no conflicts of interest to disclose.

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Study Approval
There are no animal/human subjects involved so, this study requires no institutional or ethical review board approval.

Consent Forms
NA.

Authors Contributions
MD and KUS conceptualized the study and wrote the final manuscript, EF helped with the literature search analysis and writing the first draft, FKG, AA did the literature search and review of the studies, and SA and SB supervised the whole project and wrote the final manuscript.

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