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Research Article

Formulation and Characterization of Expandable Tablet of Diacerein using Swellable Polymers

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Abstract

Some of the drugs have poor absorption because of a narrow absorption window in the gastrointestinal tract (GIT). To improve the absorption of such drugs in the GIT, gastro-retentive drug delivery techniques play an important role. Diacerein is an antirheumatic drug used for joint pain and arthritis. The expandable gastro-retentive tablets were prepared to attain an extended therapeutic action of Diacerein. Expandable tablets were formulated to prolong gastric retention, enhance the bioavailability of the drug candidate and attain a desirable size greater than the diametric size of the pyloric sphincter (i.e., 13 mm in diameter) of the tablet after administration by expandable technique. The expandable tablet was formulated using swellable polymers and polyelectrolytes, i.e., HPMCK 100, PEO, chitosan, and carbopol. The proposed expandable tablets were evaluated by preliminary evaluation parameters, micromeritic investigations, all physicochemical evaluations including swelling index, weight variation, drug content, in-vitro release studies and their release kinetics. Method: The wet granulation method is used for the preparation of expandable tablets of Diacerein. Result: The release of Diacerein from all formulations was studied in phosphate buffer pH 1.2 at 37±5°C. The net results conclude that the formulation having HPMC K 100, PEO with the addition of carbopol (formulation C1) showed the maximum swelling index as compared to others. And it was found that formulation C1 is the most superior and reliable formulation in terms of all physicochemical parameters and in-vitro drug release studies. The best formulation obtained from in-vitro drug release studies was shown.

Keywords: Gastro retentive, expandable system, noval drug delivery system, controlled drug delivery system, gastric transit time, swellable polymers, GIT.

Abbreviations:

GRDF: Gastro Retentive Drug Formulations; GIT: Gastro Intestinal Tract; GRT: Gastro Retentive Time; GET: Gastro Emptying Time; IMC: Interdigestive Myoelectric Cycle; MMC: Migrating Myoelectric Cycle; DF: Drug Formulation; NSAIDS: Non-Steroidal Anti Inflammatory Drug; SPH: Super Porous Hydrogel

INTRODUCTION

Oral route of administration is the widely accepted and most common way of drug delivery system, despite extensive in vitro release pattern characterization. In spite of, medication absorption is inadequate and extremely variable in individuals. Physiological versatility, like gastrointestinal transit and GRT, is a major issue; the later has a major impact on the overall dosage form transit.[1]At all times, the gastro retentive time period is less than 12 hours of oral controlled system[2].As a result of these aspects, a DDS that would retain in the stomach for an extended duration and be predictable was developed. According to the most recent, novel scientific study and literatures of several patents, there has been a rise in interest in innovative dosage forms that can be kept in the stomach for a longer and predictable period of time. Influencing GRT with GRDF is one of the most practical perspectives in the gastrointestinal tract (GIT), and it will open up new and essential therapeutic potentials. Preparing FDDS, imparting bio adhesion to the gastric mucosa, lowering GIT motility by corresponding consumption of medication or pharmaceutical excipients, swelling or unfolding the dosage form to a large size that limits emptying gastric, and expanding the formulation for prolonged administration are all examples of GRDFs.[3]

GRDDS benefit such drugs by increasing their [4]

Bioavailability, efficacy of the treatment, possibility of a dose reduction, conservation of stationary therapeutic levels over time, resulting in a reduction in therapeutic level fluctuation, reduced drug squandering, and the solvability of drugs that are less dissolvable in an elevated pH environment are enhanced.

1.9.1. Mechanism of expandable tablet [6, 8]

Swelling/expanding systems are pharmaceutical dosage forms that expand after being consumed, making them too large to pass via the pylorus. As a result, the dosage form takes a long time in the stomach. Because they tend to be logged at the pyloric sphincter, these systems are also known as "plug-type systems." When a polymer in the drug delivery system comes into contact with stomach fluid, it absorbs water and expands, allowing for regulated medicine release. The hydrophilic polymer network's physiochemical cross connections allow the polymer to swell significantly. This crosslink preserves the dosage form's structural integrity by preventing the polymer

from dissolving. By promoting gastric retention and maintaining a "fed" condition in the stomach, the content helps to prevent gastric waves. Swelling and expandable systems are investigated with various dose types. Even larger units have been observed being expelled from the stomach, despite the fact that they should be larger than 13 mm. Fig1.

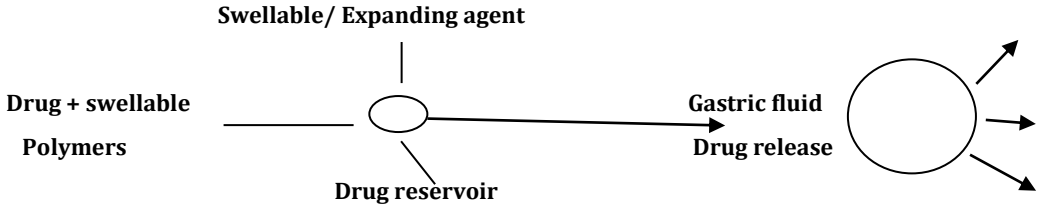

Figure 1: Schematic representation of a swelling/expanding system.

MATERIAL AND METHODS

Materials

Diacerein standard was obtained as a gift sample from AMI Life Sciences, Gujarat; HPMC K 100M, Carbopol 934,, Sodium hydrogen carbonate, and Cellulose microcrystalline were obtained from Central Drug House PVT LTD; Chitosan (middle viscous) from Sigma Life Science; Poly ethylene oxide was obtained from Across Organics, New Delhi. All additional chemicals and reagents used were of pharmaceutical ranking.

Methods

Preparation of Expandable tablet [9, 14]

The expandable gastro retentive tablet was prepared by the wet granulation method, using several proportions of drug and excipients. In preparation first, API and all the powdered excipients (excluding lubricant) were passed through a 60-mesh screen sieve to produce better sizing of particles and better flow property. According to the formula as per dose, accurately weigh API and all the excipients. The drug substance and excipients are mixed properly. Then, they prepared a binder solution for binding the particles of material, and finally mixed the binder solution with powders to form a damp mass. The granules were dried by using a hot air dryer apparatus to remove moisture, and then sized by dry screening with a 20-mesh screen. Dried granules were mixed properly with lubricant and glidant to improve the flow property of the granules and eject the tablet from the punch. Finally, granules were punched on a single-station tablet punching machine. There are a total of 11 formulations of tablets with different concentrations. (Table.1).

Table 1: Composition of total 11 formulation of tablet with different concentration

Ingredients (mg)	A1	A2	B1	B2	B3	C1	C2	C3	D1	D2	D3
Diacerein	50	50	50	50	50	50	50	50	50	50	50
HPMC K 100	50	-	30	20	25	15	20	20	15	20	20
PEO	-	50	20	30	25	15	10	20	15	10	20
Carbopol 934	-	-	-	-	-	20	20	10	-	-	-
Chitosan	-	-	-	-	-	-	-	-	20	20	10
Sod. carbonate	22	22	22	22	22	22	22	22	22	22	22
Carboxymethyl cellulose	20	20	20	20	20	20	20	20	20	20	20
Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

HPMC- Hydroxy Propyl Methyl Cellulose; PEO- Polyethylene Oxide.

Evaluation of Expandable gastro retentive tablet

Pre-formulation testing [11]

The initial phase in the natural progression of a medication's dosage forms is the pre-formulation study. It is described as a study of the physical and chemical characteristics of pharmaceuticals, both by themselves and in combination with excipients. Preformulation testing's main goal is to provide data to the formulator that will help them create stable, bio-available dosage forms. Preformulation studies were performed in the current study by taking a small amount of sample and performing various studies such as descriptions, melting points, and pH of drugs.

Analytical methodology

Preparation of Calibration curve in ethanol

The calibration curve for Diacerein was prepared by preparing a standard solution of Diacerein in a 100 ml volumetric flask, then properly weighing 10 mg of drug sample and adding 10 ml of DMA, then dissolving. This volume is made up to 100 ml with ethanol. After that, put the volumetric flask into the bath sonicator for 10 minutes, then filter the solution with watt man filter paper (stock solution). Dilution from the stock solution: pipette out 10 ml of stock solution into 100 ml of volumetric and make up the volume with ethanol, which is called the working solution. From the working solution, pipette out 1, 2, 4, 6, 8, 10 g/ml. The solution was scanned

over a range of 200–400 nm in a U.V visible spectrophotometer (Shimadzu UV–1700). The resultant max was found to be 256 nm. A calibration graph was plotted by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis.

Preparation of Calibration curve in ethanol

Preparation of simulated gastric fluid: The simulated gastric fluid of pH 1.2 was prepared using 50 ml of 0.2M potassium chloride (KCL) in a volumetric flask, then adding 85 ml of HCL and making up the volume to 200 ml with double distilled water.

KCL 0.2 M- Dissolve 14.911 gm of KCL in water and dilute with water to 1000 ml.

HCL- 7.292gm or 6.017 ml of concentrated HCL in 1000 ml volumetric flask and make up the volume to 1000 ml.

Dilutes-Accurately weighted 10 mg of medication (Diacerein) and dissolve in 10 ml of DMA and make up the volume up to 200 ml with gastric fluid containing (pH 1.2). Then shake the whole mixture and filter it out with the help of watt man filter paper. and then check the pH of the solution with the help of a digital pH meter. After that, pipette out 1,2,4,6,8,10 ml of sample in a 10 ml pipette and make up the volume up to 10 ml and check the specific absorbance**.**

Drug-Excipients Compatibility Study [12, 13]

Fourier Transform Infrared Absorption (FTIR) Spectra

FTIR analysis was used to identify the Diacerein gift sample by generating an IR spectrum of the drug sample by triturating 100mg of high grade KBr with 1 mg of Diacerein and also with other excipients, in the mortar to produce a pellet using a KBr press machine. Pallets are scanned in the FTIR at a wavelength range of 4000-400 cm^{-1}. The FTIR spectrum of the sample (Diacerein) is displayed in the picture, which is compared to the Diacerein standard spectrum mentioned in IP.

Differential Scanning Calorimetric (DSC) analysis [12]

The basic principle behind this technique is that when a sample performs a physical transformation, such as phase transitions, more or less heat must be directed to it than to the reference in order to keep both temperatures constant. A Perkin-Elmer DSC7 from the United States was used to examine the samples. Warming tests (6.510 mg) on an aluminum container in a nitrogen atmosphere were performed at a rate of (10 °C/minutes) over a temperature range of 5 to 300 °C. The experiment was carried out with a nitrogen gas stream of 20 pound per square inch (lb/in2).

Micromeritic properties [12, 13]

The microspheres were characterized by their angle of repose bulk density, tapped density, compressibility index, and Hausner's ratio.

Melting point [12, 13]

For identification of samples and purity indication in pre-formulation studies, the melting point determination is the most helpful characteristic. The melting point of a Diacerein drug sample is reported by using the digital auto melting point apparatus. The melting point of a pure sample is generally determined via the capillary fusion technique. One end of the capillary was fused with fire, and powdered medicine was manually tapped into the capillary. The already loaded capillary was then placed into the melting point mechanical assembly, which also included a thermometer. A magnifying window was used to track the medication powder as it warmed. The "liquefying point" is the temperature at which a solid begins to melt. Then it was compared with the melting point mentioned in the certificate of analysis and literature.

Physicochemical characterization of drug [12, 13]

pH determination

To determine the nature of the drug sample (acidic or basic nature). With the help of digital pH mater, it can be determined. A digital pH metre calibrated with a pH 4 buffer was used to determine the pH. To create a 1% Diacerein solution, dissolve 1 gm of Diacerein in 100 mL of distilled water. After 10 minutes, the pH electrode was immersed in Diacerein solution and the average value was recorded. Choose an average value.

Loss on drying

Water and volatile materials of any nature that may be driven out under particular conditions cause loss on drying, which is stated as a percentage of w/w. The test is performed on a well-mixed drug sample. It can be determine by keeping the known weight sample in digital moisture balance, at 80ºC.

Determination of Particle size

The dispersion of powder sample in glycerin was mounted on a glass slide and seen under a 10x magnification optical microscope. A photomicroscope RXL-ST (Carton) and a USB digital scale computer with a software program were used to measure particle size. fig.7.

Characterization of expandable granules [12, 13]

Bulk density

Bulk density is a mathematical term that refers to the amount of material in a given volume. Bulk density is influenced by particle form, cohesion, and size distribution. The initial bulk volume was determined by carefully pouring the volume of precisely weighted grains via a large funnel into a graduated measuring cylinder and measuring it. (Values in gm/cm3 units)

Bulk density =mass of a powder (w) / the volume of the powder (V1).

Tapped density

The mass of the powder divided by the volume of the tap is the tapped density. The term "tapped volume" refers to the space occupied by a given quantity of powder after a typical tapping of a measure. This can be done by accurately measuring the sample powder and placing it in a measuring cylinder having a capacity of 100 ml, then placing this on bulk density apparatus for mechanical tapping (100 times). By recording the final volume, we can estimate the tapped density (values expressed in gm/cm3).

$$\text{Tapped density} = \frac{\text{mass of powder}}{\text{Tapped volume}}$$

Carr's index (%)

Carr's index can be used to determine the flowability of a powder in most cases. According to this, a Carr index of less than 15% indicates acceptable flowability, whereas a Carr index of more than 25% indicates poor flowability. The blending flow property depends upon the compressibility index. Carr's index can be used to determine a powder's compressibility. The formula is used to calculate it. (Values are as shown in Table.2.)

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 2: Carr's index (%) and their relative flowability

Carr's Index	
% Compressibility	**Relative flowability**
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Slightly poor
28-35	Poor
35-38	Very poor
>40	Extremely poor

Hausner's ratio

The Hausner's percentage is a measure of a powder's capacity to compress. This Equation can be used to compute it. Hausner's proportion is a common way of expressing the ability of a powder to flow. Table.3 There is a value greater than one. Poor flowability is assumed. The observations used to determine flow attributes were reduced

Hausner's ratio = (Tapped density / Bulk density) × 100

Table 3: Flow character and Hausner's ratio

Flow character	Hausner ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59

Angle of Repose (θ)

The flow characteristics are determined using the angle of repose. An angle of repose is the maximum possible angle between a powder pile's surface and a horizontal surface. The fixed funnel approach was used. The graph paper was placed on a level horizontal surface with the tip of a funnel placed at a height of h above it. The grains were slowly poured through a funnel until the peak of the conical pile reached the tip of the funnel. The formula was used to determine the angle of repose. Table 4.

$$\tan \theta = h/r$$

Where: Θ, belongs to the angle of repose

h, belongs to the height of pile

r, belongs to the radius of pile

Table 4: Angle of repose and flowability

Angle of repose	Flowability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Characterization of expandable tablet [12, 13]

Hardness: A Pfizer hardness tester was used to measure toughness or tablet crushing strength (the force involved in disintegrating a tablet under diametric compression). Three tablets from each formulation were examined, and the average data was noted. The hardness mean and standard deviation parameters were estimated.

Thickness and Diameter: The diameter and thickness of the tablet were measured using a vernier calliper. Millimetres are used to measure it. Each batch received three tablet randomly picked, and the mean and standard deviation values were recorded.

Weight variation: To determine the weight variation, the individual weights of 20 tablets from each batch were weighed accurately. Then, the sample mean and standard deviation of each batch of tablets were determined.

Friability: From each batch, 20 tablets were carefully weighed and placed in the Friabilator's plastic chamber. The chamber was spun 100 times at 25 rpm for 4 minutes. The tablet drops from a distance of 6 inches after each turn. The tablet was taken out, dusted, and weighed again after 100 revolutions. The following formula was used to calculate the proportion of tablets that were friable.

$$\text{Friability} = W_i - W_f / W_i \times 100$$

W_i = initial weight of tablet before friability

W_f = final weight of tablet after friability.

Percentage drug content: A precisely measured amount of finely powdered tablet, corresponding to 50 mg of drug, was crushed and combined with 5 ml of dimethyl sulfoxide and 50 ml of methanol in a volumetric flask in order to assess the drug content of formulations. Samples were sonicated for 30 minutes to ensure full dissolution, and then filtered using Wattman filter paper, appropriately diluted with distilled water as necessary, and finally evaluated in UV by taking an absorbance measurement at 256 nm. [11, 13]

Swelling index [12, 13]

With a digital vernier calliper, the diameter of tablets was measured at intervals of 0, 0.5, 1, 2, 4, 8, 12, and 24 hours until the maximum diameter was reached. The swelling indexes (SI) were then determined using the initial diameter of the tablet (D1) and the maximum diameter after swelling in water (D2) as follows:

SI (%) = D2-D1/D1 x 100

With the help of the USP dissolution apparatus Type II, an in vitro study was performed. When it comes to procedure, in 900 ml of 0.1 N HCL (pH 1.2), maintained at 37±0.5°C at a speed of 50 rpm. At suitable time intervals, aliquots (10 ml) were withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain a constant volume for drug dissolution. After that, the sample was filtered through watt man filter paper and diluted to a suitable concentration with 0.1 N HCL. The absorbance reading was reported at 256 nm with the help of an ultraviolet spectrophotometer. The cumulative percentage of drug released was evaluated by using an equation obtained from a standard calibration curve.

Drug release kinetic study of optimized formulation [13, 14]

To assess in-vitro release data, various kinetic models were utilised to characterise the drug release kinetics.

Zero order: It defines a system in which the drug's concentration has no effect on the rate of release. [Equation (i)]

$$\mathbf{C = k_o t} \qquad \text{[Equation (i)]}$$

Where, 'k' is the zero order rate constant (concentration / time) & 't' is the time.

Plot: cumulative % drug release v/s time

First order: It describes the system release where release rate is dependent of its concentration. [Equation (ii)]

$$\mathbf{\text{Log } C = \text{Log } C_o - kt / 2.303} \qquad \text{[Equation (ii)]}$$

Where, 'C_o' is the initial concentration of drug &'k' is the first order constant

Plot: log cumulative of % drug remaining v/s time

Higuchi model: According to this definition, the mechanism by which pharmaceuticals are released from insoluble matrix is square root time-dependent and is based on fickian diffusion. [Equation (iii)]

$$Q = Kt_{1/2}$$ [Equation (iii)]

Where, 'K' is the constant reflecting the design variable of the system

Plot: cumulative % drug release v/s square root of time

Korsmeyer – Peppas model: Korsmeyer-Peppas obtained a straightforward connection that describes drug release from a polymeric system equation. The % drug released time against time was fitted in order to comprehend the process of drug release and to examine the variations in release profiles among various matrix formulations. [Equation (iv)]

$$M_t/M_\infty = k.t^n$$ [Equation (iv)]

Where, M_t/M_∞ = percent drug release at time t , 'k' is constant incorporating structural and geometrical characteristics of the sustained release device & 'n' exponential which characterizes mechanism of drug release.

Plot: log cumulative % drug release v/s log time

Comparative studies with marketed product

The best formulation (C1) was compared with the marketed formulation (GLUCOZONE TABLET, having a combination of Diacerein IP 50mg with Glucosamine & Methyl sulfonyl methane, Mfg date: Feb 2022 and Expiry date: Jan 2024, Batch No. 5562002) manufactured by Leeford Healthcare Ltd. Baddi, Distt. Solan 173205 (H.P.) for release of Diacerein (in vitro) in gastric fluid pH 1.2 to investigate the impact of Diacerein as gastro retentive in the formulation. The cumulative percentage of drug released was evaluated by using an equation obtained from a standard calibration curve.

Stability studies [12]

Stability testing is used to assess if different environmental conditions, such as light, temperature, and humidity, have an effect on a drug substance's or drug product's quality over time. The stability test was performed to look at the medication and formulation's stability. The idealised formulation (C1) was placed in a Petri dish by wrapped in aluminium foil and maintained in a humidity chamber according to ICH guidelines, at $25^0C \pm 2^0C/45$ % RH ± 5% and $40^0C \pm 2^0C/75$ % RH ± 5%. The stability investigation was carried out at the 0, 15, and 30 day. The formulation was evaluated for colour, weight fluctuation, hardness, percent drug content and % CDR of Diacerein by using UV spectrophotometer (Shimadzu).

RESULT AND DISCUSSION

Eleven batches (A1to D3) of expandable tablet were prepared by using different ratio. The Organoleptic properties of Diacerein inspected visually for identification of appearance, color, odor, nature were found to be as shown Table 5.

Table 5: Organoleptic properties of Diacerein

Organoleptic Properties	Diacerein sample	Conclusion
Appearance	Fine yellow smooth powder	The properties of Diacerein drug sample was compared and found same as given in literature.
Color	Yellow	
Odor	Odorless	
Nature	Smooth powder	

Ultraviolet Visible Spectrophotometry

Maximum absorbance (λ max) of Diacerein found to be 256 nm.

Calibration curve in ethanol

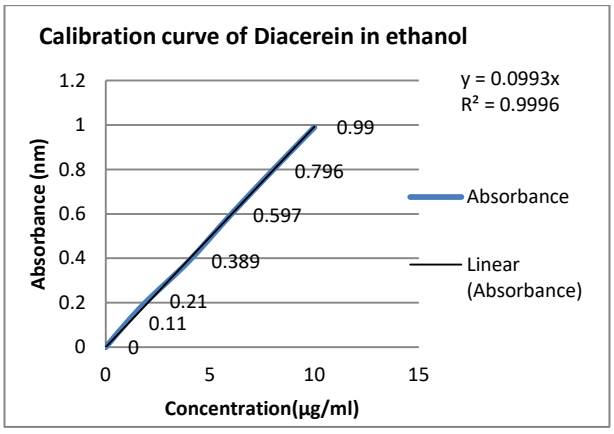

Table 6. Absorption in ethanol at different concentration.

S.No.	Concentration (ml)	Absorbance
1	0	0
2	1	0.11
3	2	0.21
4	4	0.389
5	6	0.597
6	8	0.796
7	10	0.99

Figure 2: Calibration curve in ethanol

Calibration curve in gastric fluid (pH 1.2)

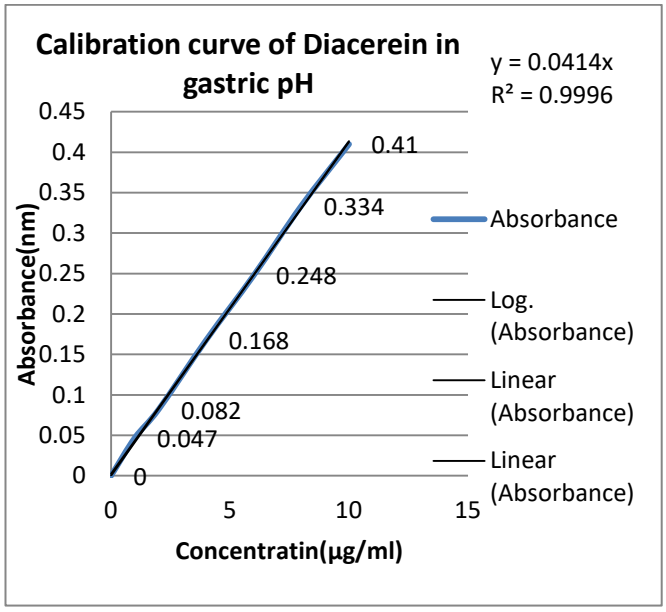

Table 7.Absorptions in 0.1 N HCL (1.2 pH) at different concentration

S.No.	Concentration (ml)	Absorbance
1	0	0
2	1	0.047
3	2	0.082
4	4	0.168
5	6	0.248
6	8	0.334
7	10	0.41

Figure 3: Calibration curve 0.1N HCL (1.2 pH)

Fourier Transform Infrared Absorption (FTIR) Spectra

FTIR spectroscopy was found that there were no major shifts in band hence; confirming that there were no interactions between drug and polymers as shown in figures Fig.4 and Fig. 5

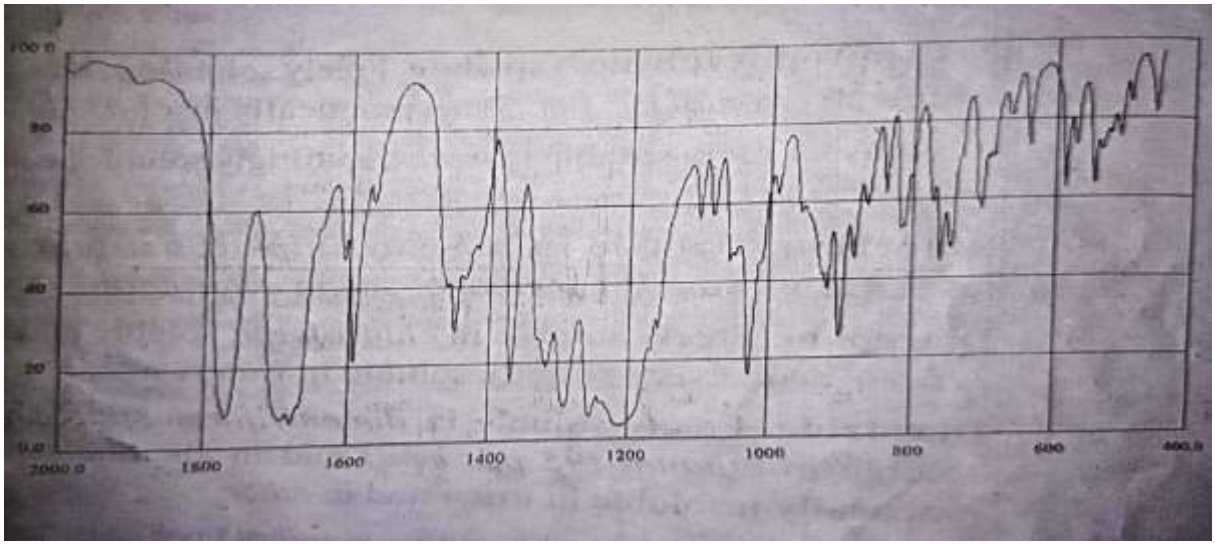

Figure 4: Standard reference FTIR spectra of Diacerein as per IP.

Characteristics peaks of Diacerein drug sample appeared at 3286.11cm^{-1}, 3043.12cm^{-1}, 2908.13cm^{-1}, 1766.48cm^{-1}, 1712.48cm^{-1}, 1515.78cm^{-1}, 752.102cm^{-1}.

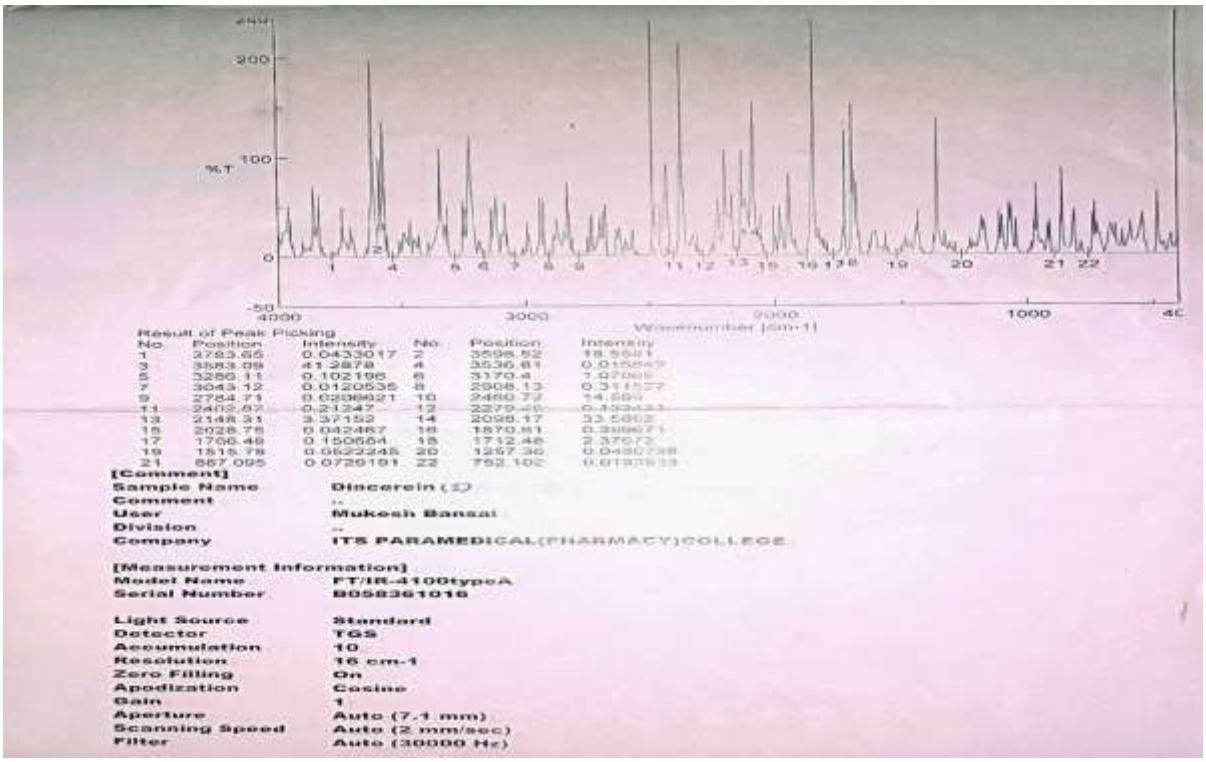

Figure 5: FTIR of Diacerein

Table 8: FTIR of Diacerein

Stretching vibrations	**Frequency (cm^{-1})**		
	Reported	**Experimented**	**Intensity**
-OH stretch broad,-COOH	3300.00	3286.11	0.102196
C-H , stretch, aromatic	3069.20	3043.12	0.0120535
C-H , stretch, aliphatic, symmetric	2935.00	2908.13	0.311527
C=O , ester	1764.56	1766.48	0.150684
C=O stretch COOH	1677.00	1712.48	2.37672
C=C stretch aromatic	1593.20	1515.78	0.0522245
C-O stretch ,COOH	1450.47	1515.78	0.0522245
m-substituted benzene	760.43	752.102	0.0183933

Differential Scanning Calorimetry (DSC) analysis

Characteristic peak onset at 247°C appeared at 254°C and ends at 255°C of Diacerein sample.

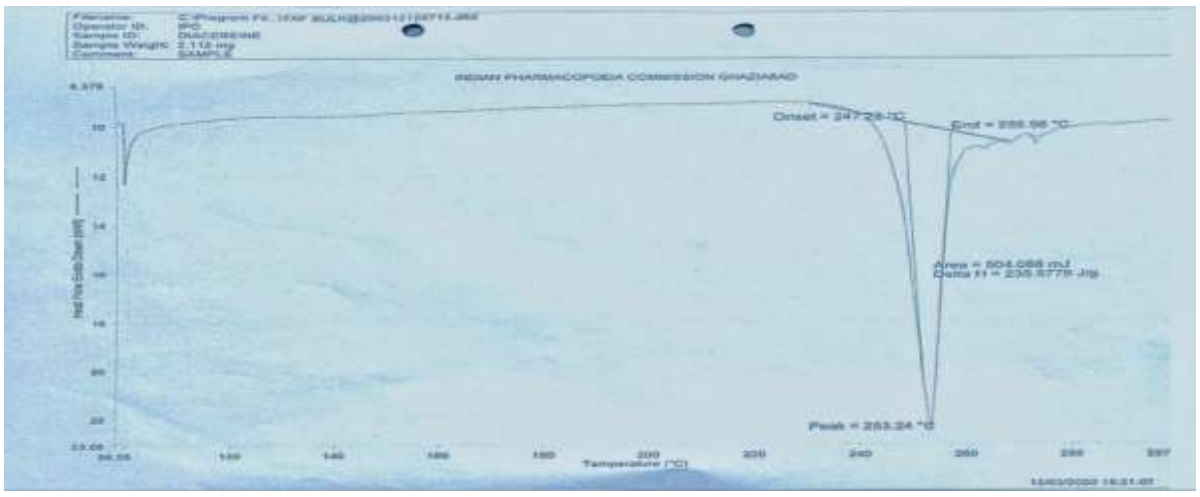

Figure 6: DSC study of Diacerein

Melting point:

The average melting point was found 220^{0}C.

Physicochemical characterization of drug

pH determination : The average pH of the drug sample was found to 6.05.

Loss on drying: The average loss on drying of the drug sample was found to 15.53% at 80^{0}C for 99 min.

Particle size determination:

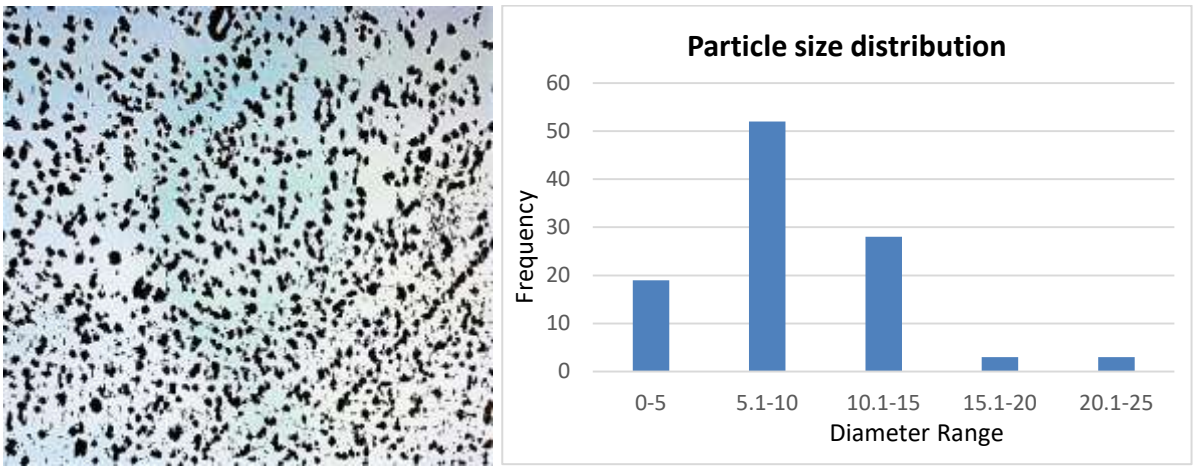

Figure 7: Pictorial and Graphical representation of particles size distribution of Diacerein

MICROMERITICS STUDIES OF GRANULES

Table 9: Micromeritics studies of granules of Diacerein

	Micromeritics study of different formulation granules										
Properties	**A1**	**A2**	**B1**	**B2**	**B3**	**C1**	**C2**	**C3**	**D1**	**D2**	**D3**
Bulk density (g/cc)	0.45	0.42	0.40	0.37	0.32	0.58	0.59	0.55	0.47	0.48	0.46
Tapped density (g/cc)	0.54	0.53	0.49	0.45	0.41	0.65	0.68	0.62	0.56	0.55	0.52
Carr's index (%)	16.67	20.75	18.36	17.63	21.9	10.7	13.2	11.3	16.7	12.72	11.53
Hausner's ratio	1.22	1.26	1.23	1.21	1.28	1.13	1.15	1.12	1.19	1.15	1.13
Angle of repose	29.46	27.17	28.20	27.25	26.84	29.34	28.51	29.01	29.4	28.3	29.01

Evaluation of expandable tablet

Table 10: Physico-chemical characteristics of Diacerein tablet

S.NO.	**Formulation code**	**Avg. Weight variation (g)**	**Avg. Hardness (kg/cm^2)**	**Avg. Thickness (mm)**	**Avg. Friability (%)**	**%Drug content**
1	A1	0.148±0.005	2.15±0.213	3.38±0.296	0.761±0.22	98.86
2	A2	0.147±0.005	2.17±0.228	3.46±0.272	0.713±0.12	98.80
3	B1	0.153±0.001	2.89±0.158	3.53±0.163	0.760±0.25	99.02
4	B2	0.151±0.002	2.95±0.211	3.85±0.127	0.728±0.13	99.06
5	B3	0.152±0.002	3.06±0.358	3.91±0.170	0.746±0.22	99.00
6	C1	0.151±0.002	3.29±0.179	3.80±0.183	0.610±0.04	99.10
7	C2	0.150±0.003	3.58±0.326	3.95±0.167	0.615±0.09	99.20
8	C3	0.151±0.002	3.45±0.243	3.92±0.174	0.675±0.04	99.09
9	D1	0.150±0.003	3.25±0.216	3.76±0.231	0.574±0.04	99.04
10	D2	0.149±0.003	3.19±0.375	3.79±0.274	0.579±0.04	99.10
11	D3	0.150±0.002	3.27±0.194	3.89±0.189	0.563±0.15	99.06

Swelling index

Table 11: Diametric measurement of Diacerein tablet before swelling and after swelling

Diameter (mm)	A1	A2	B1	B2	B3	C1	C2	C3	D1	D2	D3
D_i	8.2	8.2	8.4	8.4	8.4	8.3	8.3	8.3	8.4	8.4	8.4
D_f	12.36	12.18	12.86	12.81	12.81	13.39	13.50	13.34	13.49	13.47	13.45

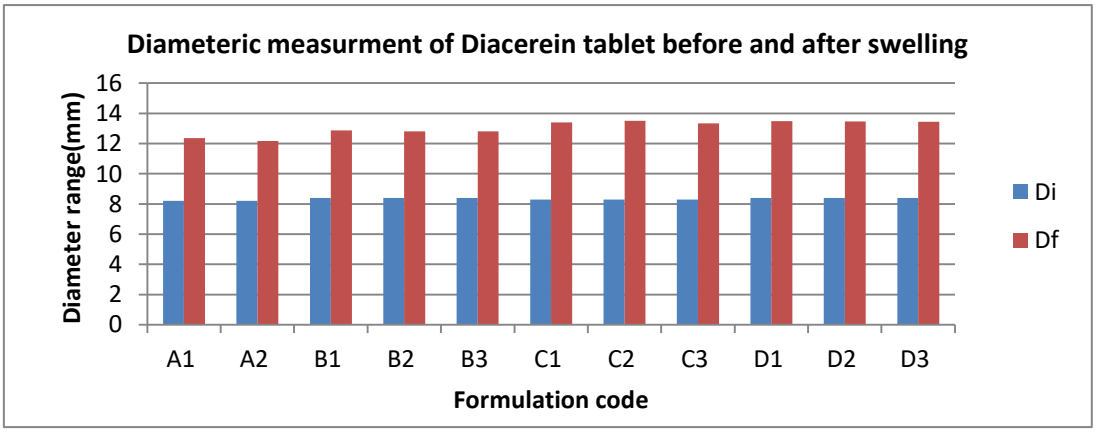

Figure 8: Graphical representation of the change in diameter of Diacerein tablet before and after swelling.

Table 12.Swelling index of Diacerein tablet

Time (hours)	Swelling index (%)										
	A1	A2	B1	B2	B3	C1	C2	C3	D1	D2	D3
0.5	15.5	15.7	15.6	15.8	16.4	18.4	18.9	18.2	14.6	14.8	13.6
1	18.6	18.4	19.8	20.6	20.4	24.8	25.6	25.9	22.8	20.6	19.5
2	22.6	22.8	24.6	24.5	24.2	32.8	33.9	35.7	36.9	34.4	32.6
4	38.5	38.4	30.5	30.4	30.8	45.9	50.9	48.6	50.6	45.6	44.6
8	50.0	48.2	52.6	52.4	52.4	60.0	62.2	60.2	60.5	60.0	58.2
12	50.6	48.4	52.8	52.4	52.4	60.2	62.4	60.4	60.6	60.2	60.2
24	50.8	48.6	53.2	52.6	52.5	60.4	62.6	60.8	60.6	60.4	60.2

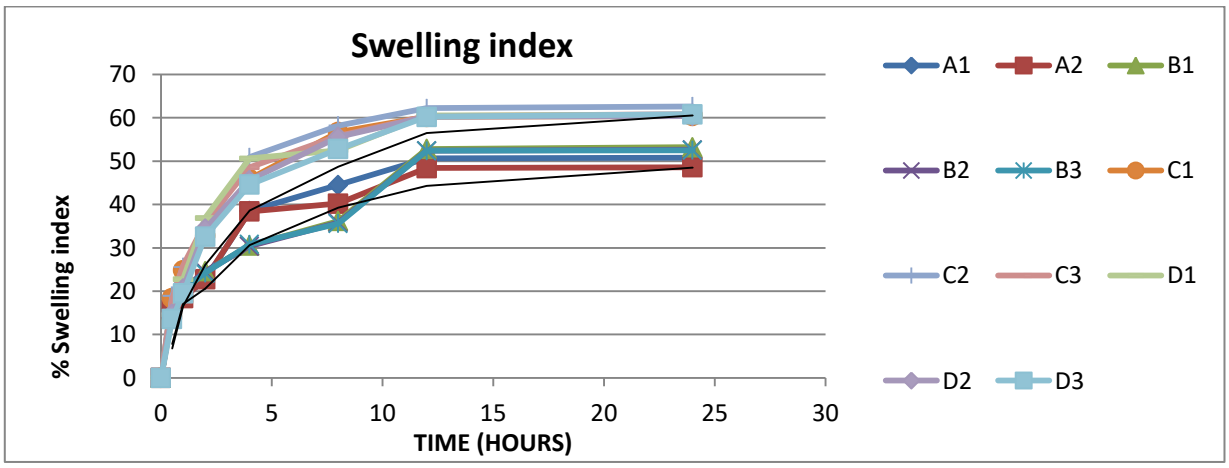

Figure 9: Percentage swelling index of different formulations with time (hrs.)

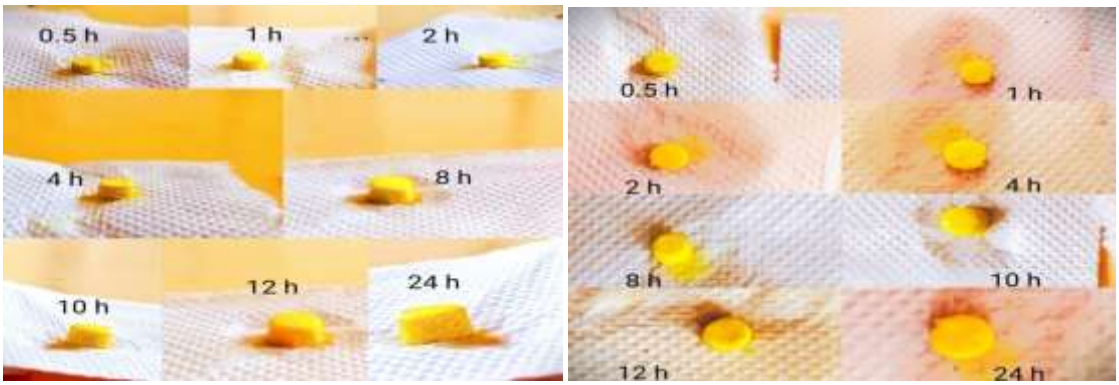

Fig.10 (a) Side view and Upper view of Swelling of expandable tablet of best formulation i.e. Formulation C1

In vitro, % drug release in gastric fluid at ph 1.2

Table 13: In vitro dissolution study of different formulation.

TIME (HRS.)	%CDR					
	C1	C2	C3	D1	D2	D3
0.25	8.86	8.78	8.51	8.3	8.4	8.2
0.5	12.76	12.86	14.37	12.5	12.6	12.3
1	17.77	16.87	20.15	16.9	16.8	17.0
2	21.31	20.42	22.64	20.1	20.2	20.0
3	24.84	25.73	29.30	25.8	25.8	25.8
4	32.92	34.18	34.64	32.7	32.8	32.6
5	42.62	42.36	42.20	38.7	38.9	40.1
8	52.4	48.42	64.84	60.4	61.3	69.3
10	73.73	73.27	73.75	68.4	70.2	75.1
12	89.71	86.6	85.32	82.6	82.6	80.0
24	94.3	90.66	88.02	88.9	87.1	86.2

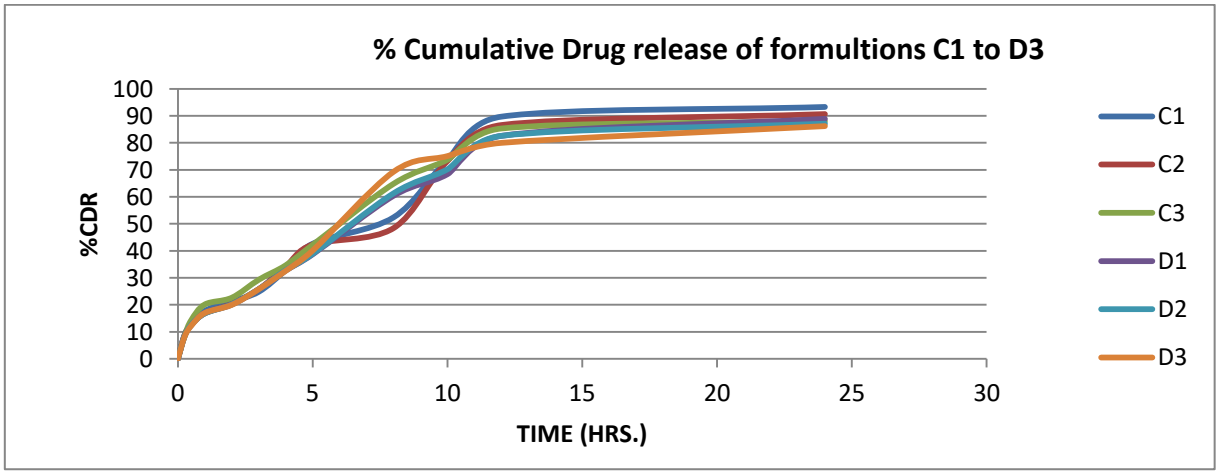

Figure 11: % Cumulative Drug release of formulation C1 to D3

Drug release kinetic study of optimized formulation

Fitting the data of formulations (C1 to D3) obtained from *In Vitro* drug release studies showed the release of Diacerein and best fitted to Korsmeyer-Peppas model as indicated by higher R^2 value. The optimum formulation (C1) has higher R^2 value as compared with other formulations.

Table 14: *In-Vitro* release kinetic study and R^2 values of formulation C1,C2 &C3.

TIME (HRS)	LOG TIME	SQRT	% CDR(C1)	LOG%CDR (C1)	% CDR(C2)	LOG%CDR (C2)	% CDR(C3)	LOG%CDR (C3)
0	0	0	0	0	0	0	0	0
0.25	-0.602	0.5	8.86	0.947	8.78	0.943	8.51	0.930
0.5	-0.301	0.707107	12.76	1.106	12.86	1.109	14.37	1.157
1	0.000	1	17.77	1.250	16.87	1.227	20.15	1.304
2	0.301	1.414214	21.31	1.329	20.42	1.310	22.64	1.355
3	0.477	1.732051	24.84	1.395	25.73	1.410	29.30	1.467
4	0.602	2	32.92	1.517	34.18	1.534	34.64	1.540
5	0.699	2.236068	42.62	1.630	42.36	1.627	42.20	1.625
8	0.903	2.828427	52.4	1.719	48.42	1.685	64.84	1.812
10	1.000	3.162278	73.73	1.868	73.27	1.865	73.75	1.868
12	1.079	3.464102	89.71	1.953	86.6	1.938	85.32	1.931
24	1.380	4.898979	93.3	1.970	90.66	1.957	88.02	1.945

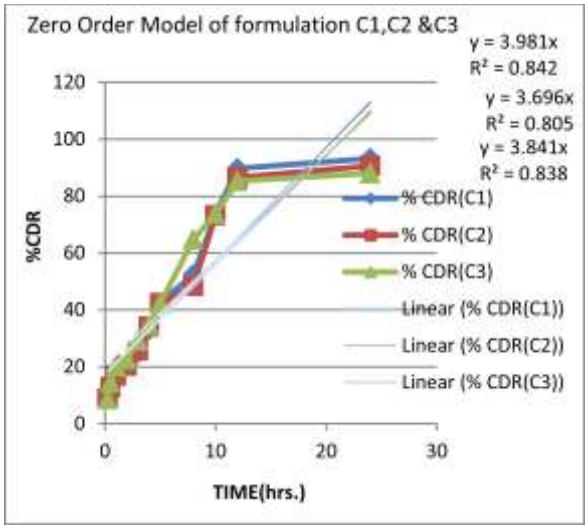

Fig.12. Zero Order Model of formulation C1, C2 &C3

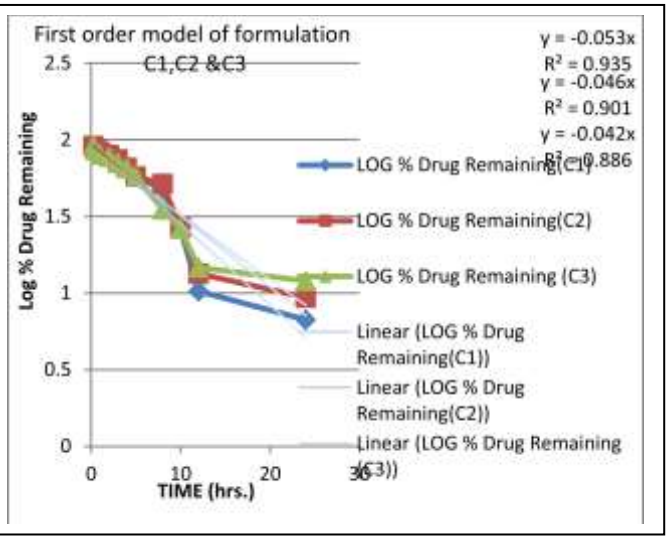

Fig.13. First order model of formulation C1, C2 &C3

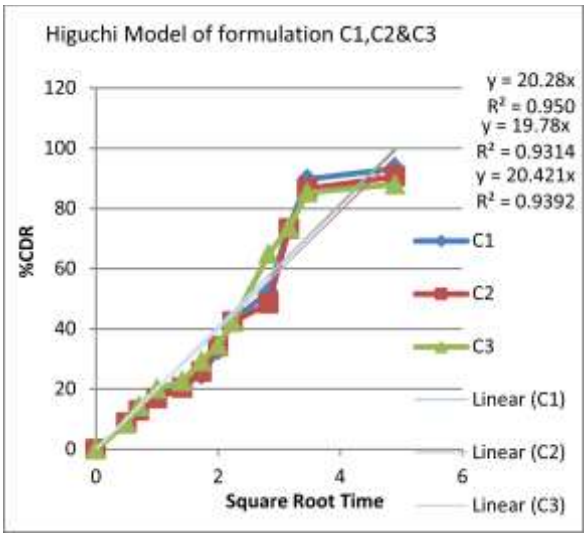

Fig.14. Higuchi Model of formulation C1, C2 &C3

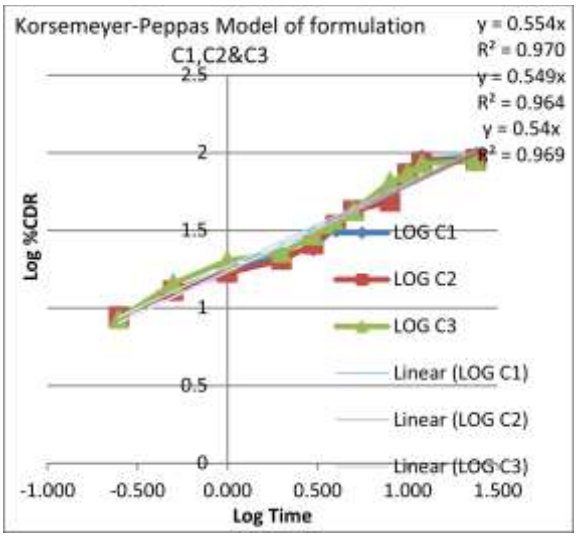

Fig 15. Korsemeyer-Peppas Model of formulation C1, C2 &C3

Table 15: *In-Vitro* release kinetic study and R^2 values of formulation C1to D3

RELEASE MODEL		C1	C2	C3	D1	D2	D3
ZERO ORDER	R^2	0.842	0.838	0.805	0.841	0.826	0.792
FIRST ORDER	R^2	0.935	0.901	0.886	0.903	0.909	0.886
HIGUCHI MODEL	R^2	0.950	0.931	0.939	0.930	0.943	0.926
KORSMEYER PEPPAS MODEL	R^2	0.970	0.964	0.969	0.962	0.967	0.961

Comparative study of optimized formulation with Marketed preparation.

Time (hrs.)	% cumulative drug release	
	Optimized formulation (C1)	Marketed formulation
s0.25	8.86	8.51
0.5	12.76	15.97
1	17.77	19.97
2	21.31	30.18
3	24.84	43.94
4	32.92	54.17
5	42.62	65.73
8	52.4	81.73
10	73.73	90.86
12	89.71	91.01
24	94.3	91.01

Table: 16. Comparison of in vitro drug release between "Optimized formulation (C1)" & "Marketed formulation".

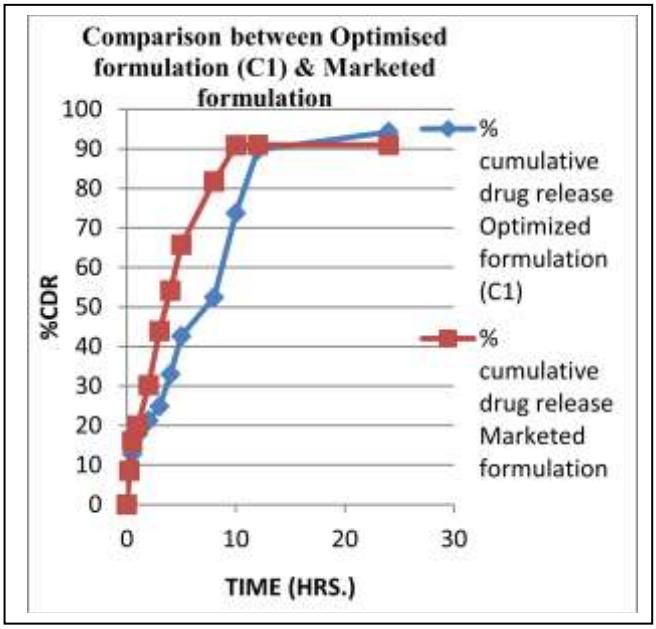

Fig 16. Comparison of % cumulative drug release between "Optimized formulation (C1)" & "Marketed formulation".

Stability study of optimized formulation

Table:17. Physical characterization of Diacerein tablet of 'formulation (C1)' at temperature $25^0C \pm 2^0C/45$ % RH ± 5% and $40^0C \pm 2^0C/75$ % RH ± 5%.

Physical parameters	Time interval(Days)					
	$25^0C \pm 2^0C/45$ % RH ± 5%			$40^0C \pm 2^0C/75$ % RH ± 5%.		
	0	15	30	0	15	30
color	yellow	yellow	yellow	yellow	Faded/dull yellow	Faded /dull yellow
Weight variation (mg)	0.151	0.151	0.152	0.151	0.151	0.152
Hardness (kg/cm²)	3.29	3.29	3.28	3.29	3.2	3.18
% drug content	99.1	99.05	99	99.1	98.5	98.02
% CDR	94.3	94	93.62	94.3	92.44	88.9

Table 18: In vitro dissolution study of 'FormulationC1' after 0, 15 & 30 days at temperature 25^{0}C ± 2^{0}C/45 % RH ± 5% and 40^{0}C ± 2^{0}C/75 % RH ± 5%.

Time (hrs.)	% CDR of optimized Formulation C1 at different time interval					
	25^{0}C ± 2^{0}C/45 % RH ± 5%			40^{0}C ± 2^{0}C/75 % RH ± 5%		
	0 day	15 days	30 days	0 day	15 days	30 days
0.25	8.86	8.51	8.51	8.86	8.51	8.51
0.5	12.76	9.76	12.42	12.76	9.76	12.42
1	17.77	14.20	14.20	17.77	14.20	14.20
2	21.31	17.75	21.31	21.31	17.75	21.31
3	24.84	24.86	24.75	24.84	24.86	25.75
4	32.92	31.97	27.54	32.92	31.97	27.54
5	42.62	42.63	35.65	42.62	42.63	34.65
8	52.4	56.84	64.83	52.4	56.84	64.83
10	73.73	73.07	75.05	73.73	71.07	79.05
12	89.71	87.5	81.87	89.71	81.75	80.87
24	94.3	94.0	93.62	94.3	92.44	88.90

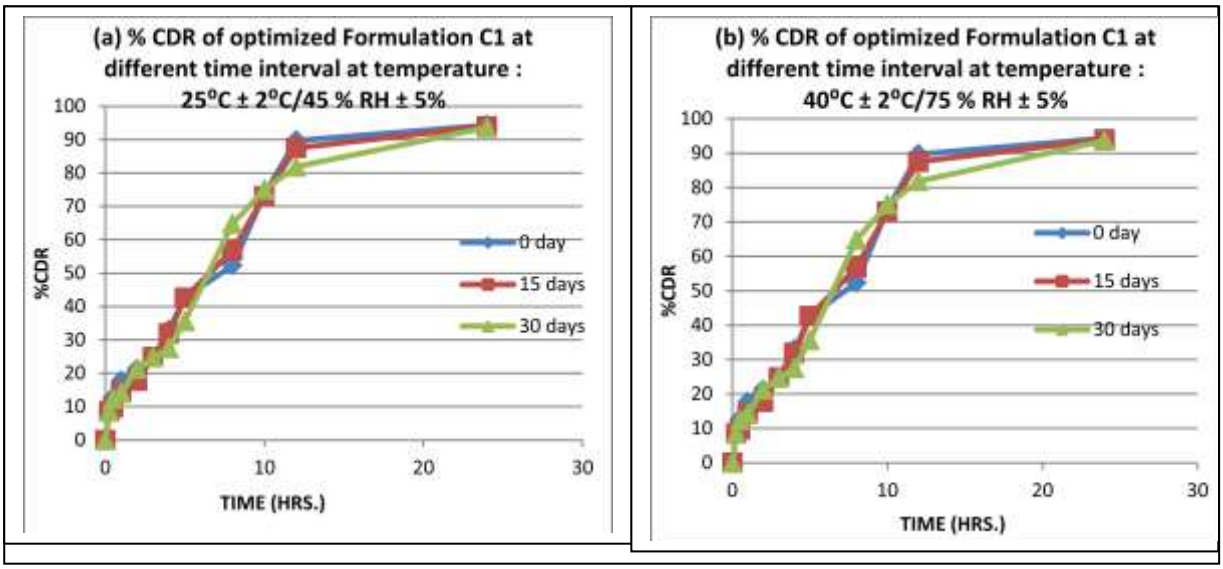

Fig.17 % cumulative drug release of Optimized formulation (C1) during 0, 15 & 30 days at Temperature: (a) 25ºC ± 2ºC/45 % RH ± 5% and (b) 40ºC ± 2ºC/75 % RH ± 5%

In the present research work, expandable gastro retentive tablets of Diacerein were formulated in different batches by using hydrophilic swellable polymers HPMC K100 , PEO (M.W.: 600) and hydrophobic polymers Carbopol 934 and Chitosan, alone and in combination of two and three, along with suspending agent and disintegrant Carboxymethyl cellulose. Corn starch was used as a binder according to the quantity sufficient. Magnesium stearate and talc are used as glidants and lubricants. Carbopol also acts as a controlled release agent and tablet binder. A total of 11 batches of expandable tablets were prepared using HPMC K 100, PEO, Carbopol 934, Chitosan, Sod carbonate and CMC in different proportions Pre-formulation studies like physical characteristics, identification tests by analytical methods; FTIR, DSC, UV, melting point ,pH determination, micromeretics etc. were carried out.The prepared tablets were evaluated for physical characteristics like hardness, friability, weight variation, swelling index, loss on drying, particle size determination, in-vitro drug release and stability studies .

The main aim was to optimise the formulation having an expandable tablet of Diacerein for the gastrointestinal drug delivery system to demonstrate the better swelling index or expandable property of the tablet by increasing the size of the tablet more than the diameter size of the pyloric sphincter, i.e., 13 mm, and optimise the formulation for 24 hr in-vitro release. It was concluded that all batches were confirmed to official requirements of hardness, thickness, friability, weight variation, and drug content. Batches C1, C2, C3, D1, D2 & D3 were deemed optimised because they demonstrated drug release for 24 hours. Because C1, C2, C3, and D1 batches had higher swelling indexes (13 mm tablet size) due to the addition of carbopol and chitosan, respectively. In an in-vitro drug release study, it was found that the formulation C1 showed maximum drug release as compared to others in the 24 hr drug release study. The optimum formulation (C1) has a

higher R2 value as compared with other formulations and is best fitted to the Korsmeyer-Peppas model as indicated by the higher R2 value. When formulation C1 was compared to marketed preparation, the optimised formulation (C1) demonstrated a 94.4 percent release in 24 hours. While marketed preparation showed a 91 % release in 12 hrs. It was concluded that formulation C1 gave maximum release with extended release and maximum gastric retention time as compared to marked preparation. The data from the table showed that the formulation was more stable at temperature $25^0C \pm 2^0C/45$ % RH ± 5% than other temperature. There was a reduction in drug content of Diacerein at higher temperature. There was not too much variation in appearance, drug content and hardness of formulation before and after storage of Diacerein tablet at $25^0C \pm 2^0C/45$ % RH ± 5% temperature. At higher temperature, there was a little variation in appearance, hardness and drug content. Therefore it was concluded that at condition like $25^0C \pm 2^0C/45$ % RH ± 5% the drug almost same and stable.

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