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Formulation and characterization of mucoadhesive microspheres of curcumin used in inflammation

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ABSTRACT: Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. Microspheres (MS), which are emulsion cells or solid particles dispersed in a continuous phase, have been utilized in various industries such as foods, cosmetics and pha rmaceuticals with an objective to Good stable and better formulation. Microspheres were evaluated for Pre formulation studies before formulating i.e. Organoleptic characteristics, Melting point, Solubility studies, Partition coefficient, Drug-polymer interaction study, Fourier transform-infrared (FT-IR) spectroscopy. Chitosan microspheres are prepared by solvent evaporation technique. Post formulation studies i.e. Drug loading, Entrapment efficiency, Production yield of microspheres, Particle size analysis, Drug release, and swelling index of the mucoadhesive microsphere of curcumin was performed and found satisfactory result.

Keywords: Mucoadhesive microspheres, Curcumin, Inflammation, Chitosan,

I. INTRODUCTION:

Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). The systems remain in close contact with the absorption tissue and attached with the mucous membrane and releasing the drug at the action site that enhance bioavailability and it can be produce both local and systemic effects. [1]

Microspheres (MS), which are emulsion cells or solid particles dispersed in a continuous phase, have been utilized in various industries such as foods, cosmetics and pharmaceuticals, etc. Emulsions are dispersed multiphase systems consisting of two or more almost mutually insoluble liquids, with the dispersed phase present in the form of droplets in a continuous phase. [2] It is anticipated that the MS with Monodispersibility may exhibit higher quality and stability than that produced by conventional techniques.

Microspheres are sometimes referred to as micro-particles dosage forms that can precisely control the release rate and target drugs to a specific body site, have created enormous impact on the formulation and development of novel drug delivery system. The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. Various mucoadhesive dosage forms such as discs, microspheres, and tablets have been prepared and reported by several research groups. [3] Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner. Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers with pharmaceutical formulations such as microspheres along with the active pharmaceutical ingredient (API). It is the reliable means to deliver the drug to the target site with specificity.[4]

Curcumin, also known as diferuloylmethane, is an active component in the golden spice turmeric Curcuma longa and in Curcuma xanthorrhiza oil. It is a highly pleiotropic molecule that exhibits antibacterial, anti-inflammatory, and hypoglycemic, antioxidant, wound- healing, and antimicrobial activities. [5]. Due to these properties, curcumin has been investigated for the treatment and supportive care of clinical conditions including proteinuria, breast cancer, multiple myeloma, depression, and cancer . Curcumin mediates potent anti-inflammatory agent and anti- carcinogenic actions via modulating various signaling molecules. It suppresses a

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number of key elements in cellular signal transduction pathways pertinent to growth, differentiation, and malignant transformation. It was demonstrated in-vitro that curcumin inhibits protein kinases, c- Jun/AP-1 activation, prostaglandin biosynthesis, and the activity and expression of the enzyme cyclooxygenase (COX)-2 [6]. Inflammation in body encounters an offending agent (like viruses, bacteria or toxic chemicals) or suffers an injury, it activate immune system. Inflammatory cells and cytokines substances stimulate more inflammatory cells. [7] These cells begin an inflammatory response to trap bacteria and other offending agents or start healing injured tissue. The result can be pain, swelling, bruising or redness. But inflammation also affects body systems**.** Inflammation is a process by which your body's white blood cells and the things they make protect you from infection from outside invaders, such as bacteria and viruses. Inflammation is an essential part of your body's healing process. It occurs when inflammatory cells travel to the place of an injury or foreign body like bacteria. If inflammatory cells stay too long, it may lead to chronic. [8].

II. MATERIALS:

Curcumin, carbopol 940, chitosan, piperine, grade solvents and reagents.

III. PRE-FORMULATION:

Pre-formulation studies is the preliminary investigation of drug and other ingredient before developing any pharmaceutical product in order to get stable, safe and effective dosage forms. The following pre-formulation studies are carried to get the initial information of the drug and excipients. [9].

3.1 Organoleptic characteristics:

I. **Colour:** less quantity of pure Curcumin is taken in butter paper and viewed in well illuminated place [10].

II. **Odour:** very less quantity of Curcumin as well as smelled place.

III. **Taste:** very less quantity of Curcumin is used to get taste with the help of tongue as well as smelled place [11].

3.2 Melting point: By putting a little amount of the medicine in a capillary tube with one end and placed it in Thiele's melting point apparatus, and recorded the temperature at which the drug starts to melt, the melting point of the drugs determined [12].

3.3 Solubility studies: The solubility of drugs tested in distilled water, a number of buffer solutions (pH 4.0, pH 7.4, and pH 8.0), and methanol. Three identical readings used to calculate the average [13].

3.4 Partition coefficient: To calculate the partition coefficient of drugs, n-octanol and water utilized in equal parts in a separating funnel. A drug solution prepared, and 1 ml added to a 50/50 mixture of n-octanol and buffer solution (pH 7.4) in a separating funnel. The mixture then be stirred for 10 minutes, let to stand for an hour, and then continued for another 24 hours. Following this, the aqueous and octanol phases centrifuged for 10 minutes at 2000 rpm to separate them. Using a UV-Vis Spectrophotometer, the aqueous and n-octanol phases measured at their respective maximums before and after partition in order to estimate the partition coefficient [14].

3.5 Determination of wavelength: UV-Vis spectrophotometry used to find the absorbance of drugs. Curcumin 10µg/ml solution was scanned in UV spectrophotometer in the range of 200-800 nm. Methanol was used as blank. Wavelength corresponding to maximum absorbance of curcumin in methanol was observed at 422 nm.

3.6 Drug-polymer interaction study: Fourier transform-infrared (FT-IR) spectroscopy In order to assess the Drug-polymer interaction study, Fourier transform-infrared (FT IR) spectroscopy study employed. The pellets scanned in 128 scans with a resolution of 4 cm^{-1} and a 1 cm^{-1} interval over a wave number range of 4000-400 cm^{-1} in an inert atmosphere.[15]

IV. FORMULATION DEVELOPMENT

Table 01 Formulation batches of Carbopol 940 microspheres of Curcumin.

Formulation Code	Drug (mg)	Carbopol 940 (mg)	chitosan (mg)	Drug Polymer ratio (w/w)	Stirring speed (rpm)
N1	500	100	100	5:1:1	1700
N2	500	100	200	5:1:2	1700
N3	500	100	300	5:1:3	1700

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N4	**500**	**100**	**400**	**5:1:4**	**1700**

Procedure: Chitosan microspheres were prepared by solvent evaporation technique. The chitosan solution (1% w/v) prepared in aqueous glacial acetic acid by continuous stirring using a sharp blade mechanical stirrer, this solution filtered through 0.45 µm milipore filter paper then the drug dispersed in the polymeric solution and stired. Sufficient amount of 25% (v/v) aqueous glutaraldehyde (cross-linking agent) added slowly with continuous stirring. The solution fed to the nozzle with a peristaltic pump, atomized by the force of compressed air and blown together with heated air to the chamber where the solvent in the droplets will be evaporated.

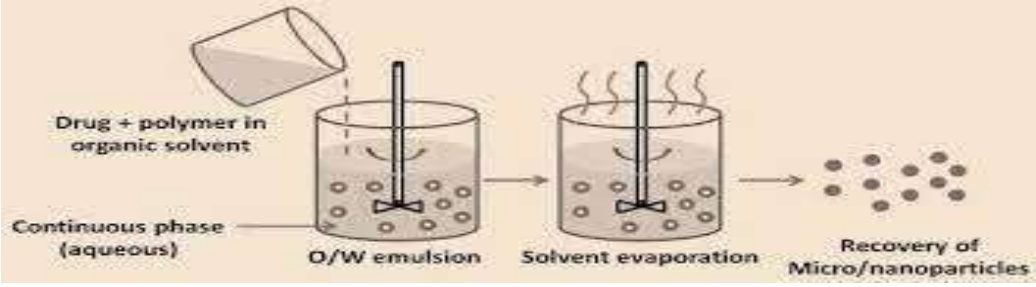

Fig. 01 Solvent evaporation method

V. EVALUATION OF MUCOADHESIVE MICROSPHERES

5.1 Production yield: The production yield of various microsphere formulation batches were determined by calculating the percentage of weight obtained after drying the final product (formulation) with respect to the initial weight of curcumin and carbopol 940 polymers. [16].

$$\% \text{ Production yield} = \frac{\text{Practical mass (final product)}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

5.2 Drug loading: The weighed amount of curcumin in the microsphere of each formulation was extracted in double distilled water on a mechanical shaker for 24 hrs. Duration to extract the entrapped drug completely. The solution was filtered through Whatman filter paper no. 41.1 mL of this solution was withdrawn and diluted to 10 mL with double distilled water. This solution was assayed for the drug content by UV-Vis spectrophotometer at 427 nm. [17].

$$\% \text{ Drug loading} = \frac{\text{Actual amount of drug loaded in microspheres}}{\text{Weighed quantity of microspheres}} \times 100$$

5.3 Entrapment efficiency: The drug loaded microspheres (100mg) were crushed in a glass mortar pestle and was dispersed in 100ml of methanol. The resultant dispersion was kept for 24 hrs for complete mixing and filtered through whatman filter paper. The drug content was determined UV specrtophotometrically after appropriate dilutions at 422 nm. The drug entrapment efficiency was calculated by the following equation

$$\% \text{ Entrapment efficiency} = \frac{\text{Mactual}}{\text{Mtheoretical}} \times 100$$

5.4 Particle size analysis: For the determination of particle size, a microscopic image analysis technique was utilized. The prepared microspheres were suitably dispersed on a microscope slide of standard dimension and the microscopic field was scanned by a video camera. The software analyzed the images that lie within the scanned field. [18].

5.5 Degree of swelling: The swell ability of the curcumin microspheres in the physiological media was determined by allowing the formulations to swell in the phosphate buffer pH 6.8 & pH 7.4. An accurately weighed amount of microspheres were immersed in little excess of phosphate buffer pH 6.8 & pH 7.4 for 24 hr. duration and washed thoroughly. The degree of swelling was calculated using the following

Formula:

$$\alpha = (Ws - Wo) / Ws$$

$$I = \alpha \times 100$$

Where, α = degree of swelling; Ws = weight of microspheres after swelling; Wo = initial weight of microspheres; and I = % swelling index.

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5.6 Mucoadhesive Test: 10 mg of microspheres was dispersed in mucin solution having different concentration (100 µg/ml, 200 µg/ml. 300 µg/ml and 400 µg/ml), incubated at 37°C for specified time (30 min, 60 min. 120 min. and 180 min.) and centrifuged at 10,000 rpm for 30 min. The remaining free mucin in the supematant was determined at 257 nm by UV spectrophotometer. The % mucin binding efficiency of microspheres was calculated using the following formula. [19]

$$\% \text{ Mucin binding efficiency} = \frac{co - cs}{co} \times 100$$

Where, C_o is initial concentration of mucin and C_s is the concentration of free mucin in the supematant.

5.7 Scanning electron microscopy (SEM): The microspheres were analyzed for their surface morphology under both 400x and 2000x magnifications under a scanning electron microscope. The surface morphology was determined by powdering the gold-coated (4A° thickness) microspheres over the double-sided tape placed on the aluminum stub of the SEM chamber system. The photomicrographs of the developed microspheres were taken at an operational accelerating voltage of 6 kV.

5.8. In-vitro drug release study: Glass-fabricated Franz diffusion cell was employed for the in vitro drug release study of the fabricated microspheres. The diffusion barrier of the dialysis membrane was employed. The dialysis membrane was equilibrated by cautiously dispersing the fabricated mucoadhesive microspheres into the donor compartment. The phosphate buffer solution of pH 6.8 & pH 7.4 was filled into the receptor compartment. The donor compartment was kept in a way that it comes in contact with the receptor compartment containing the diffusion medium. The circulating water bath helped in maintaining the temperature of 37±1°C. From the receptor compartment, the samples were withdrawn periodically and the sink condition was maintained. The samples were analyzed at 427 nm in the UV spectrophotometer. [20].

5.9 Drug release kinetics: To study the release kinetics of curcumin oral mucoadhesive batches, the data obtained from plotted in a variety of kinetic models, where:

- **Zero-order** is represented as the rate of the cumulative amount of drug released (Eq.1)

$$C = K_0 t \quad \text{..... (1)}$$

where K_0 is the zero-order rate constant expressed in units of concentration/ time and t is the time in minutes. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

- **First-order** is presented as the rate of Log cumulative % of remaining drug (Equation 2)

$$\text{LogC} = \text{Log}C_0 - K_t/2.303 \quad \text{..... (2)}$$

Where C_0 is the initial concentration of the drug, K is the first order constant and t is the time.

- **Higuchi's model** is depicted as the squared rate of cumulative % of drug released (Eq. 3)

$$Q_t = K_t^{1/2} \quad \text{..... (3)}$$

Where Q_t is the amount of drug release in time t, K is the kinetic constant and t is the time in minutes.

- **Korsmeyer-Peppas exponential model** is Log rate of Log cumulative percentage of drug released (Equation 4).

$$Mt = M1 ¼ Kt^n \quad \text{..... (4)}$$

The release exponent n and K value were calculated through the slope of the straight line. If the exponent n = 0.43 then the drug release mechanisms Fickian diffusion, if 0.43<n<0.85 then it is non-Fickian or anomalous diffusion, if n <0.85 mechanism is non-Fickian case-II diffusion. [21].

VI. RESULTS AND DISCUSSION

6.1 Organoleptic characteristics:

- **Color –** yellow
- **Odor -** odorless,
- **Taste –** characteristic taste

6.1.2 Melting point study: The melting point of Curcumin was found to be in the range of 183-184°C.

6.1.3 Solubility study: Curcumin was found to be most soluble in petroleum ether, ethanol and methanol indicating non-polar.

Table 02. Solubility profile of Curcumin.

S. No.	SOLVENT	SOLUBILITY PROFILE	INTERPRETATION
1.	Ethanol	+++	Soluble
2.	Methanol	+++	Soluble
3.	Ethyl acetate	+++	Soluble
4.	Distilled water	++	Low solubility
5.	Petroleum ether	++++	High solubility

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6.	Acetone	+++	Soluble

6.1.4 Partition coefficient study: The partition coefficient was found to be 1.21 and indicating lipophilic behavior

6.1.5 Determination of absorption maxima: the λmax of Curcumin was found to be 425 nm (**Figure 6.1**).

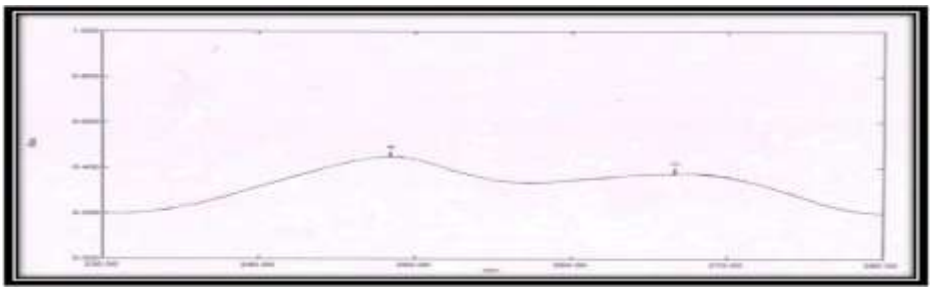
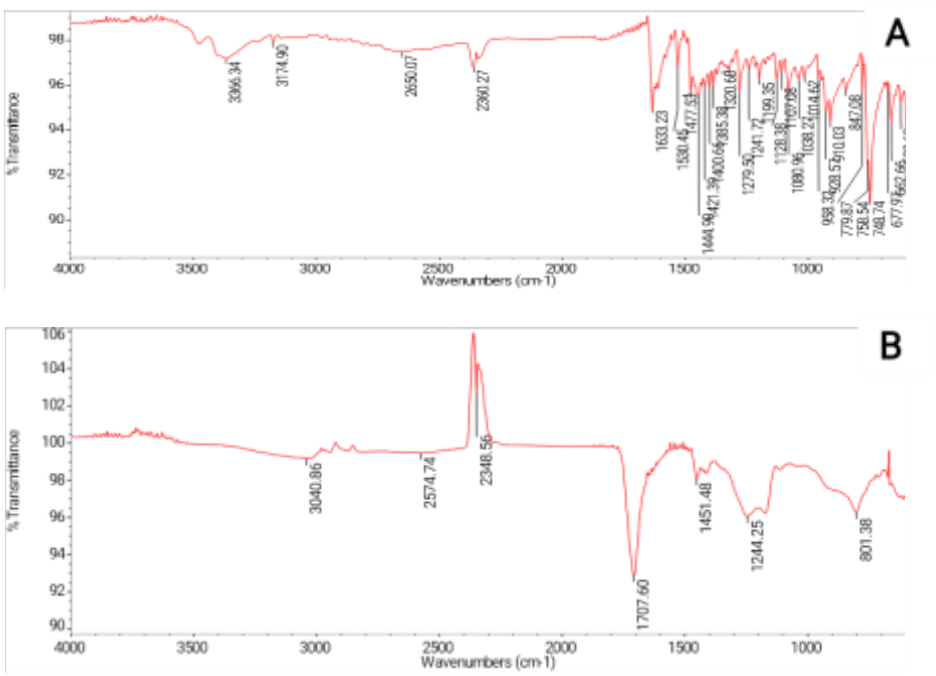


Figure 02. UV-Vis spectra of Curcumin.

6.1.6. FT-IR spectroscopy

The FT-IR spectra of pure Curcumin. drug (**Figure 3.A**), carbopol 940 (**Figure 3.B**), and mucoadhesive microspheres (**Figure 3.C**) were recorded which revealed no possible interactions between the drug and mucoadhesive polymers. There was no substantial modification in the positions of characteristic absorption bands and bonds of diverse functional groups present in the drug, indicating no such drug-excipients interactions. In the physical mixture and optimized formulation, the drug remained in pure, unchanged, and non-interactive state. The results stated that Curcumin was compatible with carbopol 940.



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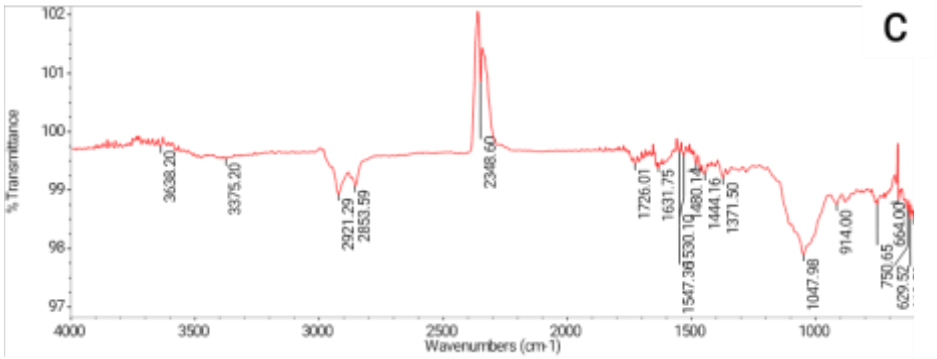

Figure 3 FT-IR spectra of (3.A) Drug; (3.B) Polymer; (3.C) Formulation

6.2 Formulation evaluation

6.2.1 Production yield (%): The production yield of microspheres were found to be in the range of 81.4-98.42% (**Table 2**). It was found that the production yield of the mucoadhesive microspheres was higher for Carbopol 940. The plausible cause following the difference in yield may be due to the high viscosity offered by the carbopol solution which may decrease its syringability resulting in the needle orifice blockade and leading to drug-polymer solution wastage, which eventually leads to decrease in the production yields. Another probable reason for that reduced yield may be the sticking and agglomeration of the polymeric contents to the wall of the beaker and the blades of the stirrer during the microsphere formation.

6.2.2 Drug loading (%): The drug loading formulated curcumin microspheres were found to be the range of 77.84±0.36 - 73.96±0.46 (%) respectively (**Table 03)**. The N1 batch has the highest drug loading

6.2.3 Entrapment efficiency (%): The entrapment efficiency of formulated Curcumin microspheres was found to be in the range of 79.55±0.14 - 72.42±0.26 % respectively (**Table 03)**. The N1 batch has the highest entrapment efficiency than other batches. It was scrutinized that with the increase in the concentration of mucoadhesive polymer, the entrapment efficiency increases simultaneously at higher and lower levels of stirring rate. Though, it was distinguished that carbopol 940 had higher influence over entrapment efficiency, owing to the higher molecular weight of carbopol 940 which promotes the formation of more intact matrix network.

6.2.4 Particle size analysis: The average size of the fabricated mucoadhesive microspheres were in the range of 15-31 µm which is an optimized size for oral administration. The rate of stirring had a key influence over the particle size. It was detected that with the increase in the stirring rate, the particle size decreases abruptly, irrelevant of the mucoadhesive polymer concentration (**Table 03**).

6.2.5 Swelling property: The swelling index of the mucoadhesive microsphere ranged from 0.54-0.89. In the study, carbopol microspheres exhibited higher degree of swelling which may be due to higher molecular weight of the former polymer. However, a clear cut conclusion was not produced. With the increase in the concentration of mucoadhesive polymer, a slight increase in swelling was observed. Similarly, a minor decline in the swelling attributes were observed at the lesser mucoadhesive polymer concentration which perhaps because of the higher level of ethyl cellulose, the film forming polymer in the formulations that allows slighter diffusion of water within the polymeric matrix (**Table 03**).

Table 03 Evaluation parameters of Curcumin microspheres

F.code	Production yield (%)	Drug loading (µm±sd) (%)	Entrapment efficiency (µm±sd) (%)	Average particle size (µm±sd)	Degree of swelling (µm±sd)	Mucoadhesion (µm±sd)
N1	84.64	77.84±0.36	79.55±0.14	25.22±1.64	0.89±0.15	99.56±1.04
N2	89.24	74.34±0.54	77.98±0.17	15.54±0.94	0.87±0.06	98.12±0.61
N3	81.40	73.90±0.42	76.10±0.43	30.98±1.54	0.84±0.21	96.23±1.27
N4	87.45	73.96±0.46	72.42±0.26	18.72±1.52	0.83±0.05	97.89±0.66

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Values expressed as mean ± SD, n=3

6.2.6 Morphological studies The optimized formulation was investigated by SEM for studying the morphology and surface characteristics of prepared mucoadhesive microspheres. The photomicrograph of the microspheres illustrated that the particles were well separated with spherical shape having attached drug particles (**Figure 04 A**). This suggested that the entire drug was found uniformly over the surface of the separated microstructures. The deep crevices and pinholes were observed, which may be due to the air bubble bursting during the drying process (**Figure 04 B**). [22,23]

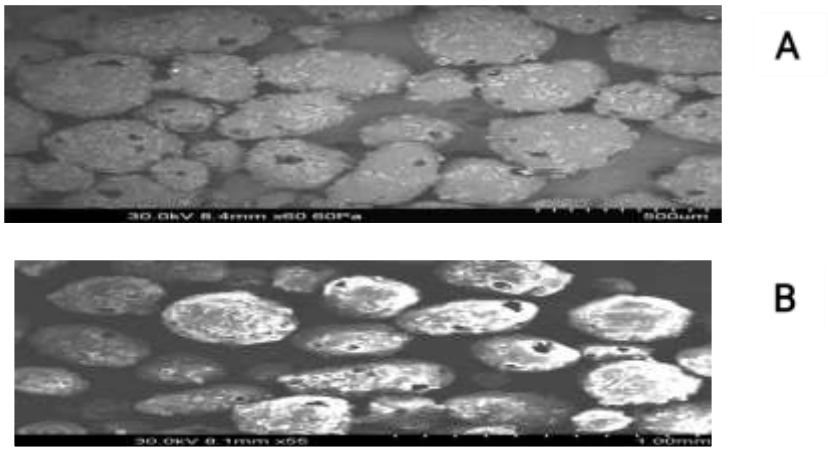
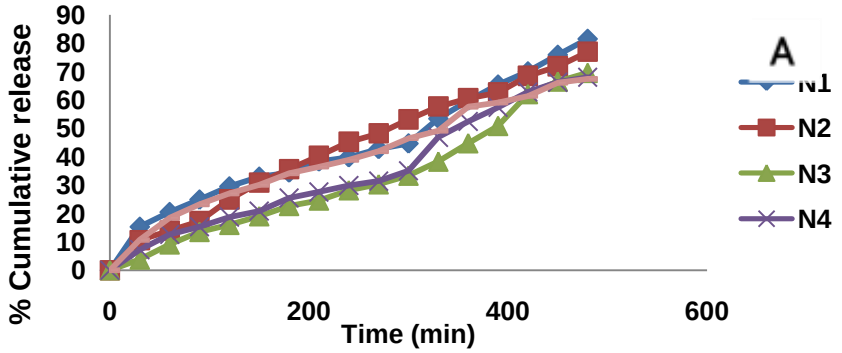


Fig. 04 Scanning electron photomicrograph: (A) at 60x magnification; (B) at 55x magnification.

6.2.6. In-vitro drug release study The drug release profile of Curcumin from various batches of microspheres at pH 6.8 & pH 7.4 phosphate buffer demonstrated significant drug release in the range of 70.5-81.5%. The selected optimized batch of formulation had highest cumulative release 81.50% as compared to other formulations (**Graph 01. A**). The ratio of polymeric content, mucoadhesive polymers content, film forming polymer, particle size, and formulation technique had critical influence on drug release. The optimized formulation N1 expressed best drug release. [24]



Graph no. 01: Characterization of microspheres: (A) in-vitro drug release study.

6.2.7 Drug release kinetics: The analysis of in-vitro drug release data indicates that the Curcumin release from the microspheres followed zero order kinetics in most of the batches like N1, N2, N3, and N4 as the correlation coefficient 'r' values in the zero order model were higher than the other model. The overall kinetic study supported the diffusion mode as the primary phenomenon of drug release [25]. The results of kinetic treatment applied to release profile of formulation N1 to N4 are shown

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in Table 04.

Table 04 Kinetic treatment of drug release profile of optimized formulations

Formulation code	Mathematical models				
	Zero order	First order	Higuchi	Korsemeyer-Peppas	Best fit model
N1	0.966	0.593	0.928	0.467	Zero order
N2	0.985	0.657	0.928	0.482	Zero order
N3	0.991	0.762	0.927	0.444	Zero order
N4	0.991	0.680	0.962	0.430	Zero order

VII. CONCLUSION

The current research attempted at rationally formulating a mucoadhesive microparticulate system for the inflammation drug Curcumin for oral administration with a perspective of improving the bioavailability of the drug. The research suggested that solvent evaporation remained the most relevant procedure for the fabrication of mucoadhesive microspheres of Curcumin based on mucoadhesive polymers. The particle size analysis indicated that all the fabricated formulations have particle size in the range of 15-31 µm which is most convenient for the oral administration of the prepared formulation for enhancing bioavailability. The SEM photomicrograph displayed spherical and smooth surface morphology of the formulations. From the studied parameters it can be concluded that carbopol 940 & chitosan offered better mucoadhesive attributes for the formulating Curcumin oral mucoadhesive microspheres. Thus, the formulated microspheres could be a potential carrier for elevating the bioavailability oral route.

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