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DESIGN OF EXPERIMENTS (DOE) FOR THE DEVELOPMENT AND EVALUATION OF EMPAGLIFLOZIN-LOADED MICROSPHERES

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ABSTRACT
The present study aimed to formulate and evaluate Empagliflozin microspheres using the solvent evaporation technique to develop a sustained-release oral drug delivery system for improved therapeutic efficacy and patient compliance in the management of Type 2 Diabetes Mellitus. Eight formulations (F1–F8) were prepared using varying concentrations of sodium alginate and ethyl cellulose as release-retarding polymers. Prior to formulation, preformulation studies including organoleptic evaluation, solubility, melting point determination, UV spectrophotometric analysis, and FTIR compatibility studies were carried out. Empagliflozin exhibited a λmax at 225 nm, and FTIR studies confirmed the absence of significant drug–excipient interactions, indicating good compatibility. The prepared microspheres were evaluated for particle size, zeta potential, percentage yield, surface morphology, drug entrapment efficiency, in-vitro drug release, release kinetics, and stability. The particle size ranged from 746 to 869 µm, while zeta potential values ranged from −20 to −36 mV, indicating acceptable physical stability. Percentage yield varied between 72.59% and 85.59%, and drug entrapment efficiency ranged from 76.39% to 92.53%. Scanning electron microscopy revealed spherical, discrete microspheres with smooth surfaces. Among all formulations, F8 exhibited the best performance with a particle size of 746 µm, zeta potential of −24 mV, percentage yield of 85.59%, and drug entrapment efficiency of 92.53%. In-vitro dissolution studies demonstrated sustained drug release over 8 hours, with formulation F8 achieving the highest cumulative drug release of 98.22%. Drug release kinetic analysis showed that the optimized formulation followed Zero-order kinetics (R^2 = 0.984), indicating nearly constant drug release with diffusion contributing to the release mechanism. Stability studies performed for 90 days under ICH-recommended conditions revealed no significant physical changes and only a slight reduction in drug release, confirming the stability of the optimized formulation. The study concludes that the solvent evaporation technique is an effective approach for preparing Empagliflozin microspheres with excellent encapsulation efficiency, sustained drug release, and satisfactory stability. The optimized formulation (F8) demonstrated promising characteristics as a sustained-release oral delivery system that may improve bioavailability, reduce dosing frequency, and enhance patient compliance. Further in-vivo pharmacokinetic and pharmacodynamic studies are recommended to establish its clinical applicability.

KEYWORDS: Empagliflozin, microspheres, pharmacokinetic and pharmacodynamic studies.

INTRODUCTION
NOVEL DRUG DELIVERY SYSTEMS
Novel drug delivery systems can include those based on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms also referred as controlled drug delivery systems include osmosis, diffusion, erosion, dissolution and electro transport. Biochemical mechanisms include monoclonal antibodies,

gene therapy, and vector systems, polymer drug addicts and liposomes. Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) Passive and (ii) Active targeting.

MICROSPHERES

Microspheres can be characterized as solid, approximately spherical particles with a diameter having between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape. Both the terms microcapsules and microspheres are often used as synonyms. Medication That is simply transmitted in from gastrointestinal tract (GIT) and also has a short half-life is immediately destroyed from circulatory system in the blood. The intake dose is delivered in several tiny different for multiparticulate particles, which hold and discharge a part of the dosage; therefore the breakdown of a specific subunit does not affect the whole dosage failure. Micro particles used in skin applications required to benefit the release of the mediction into the skin ensure that now the drug remains localized at the application site and does not enter the systemic circulation unnecessarily. They act as a reservoir which releases an active ingredient over a longer period of time to maintain effective concentration of drug products in the skin while decreasing undesired side effects. Consequently, cycles of over- and under-medication are reduced. It is especially relevant for the reduction of antimicrobial resistance in the management of infectious diseases. These distribution mechanisms can also boost product safety or integration into appropriate vehicles.

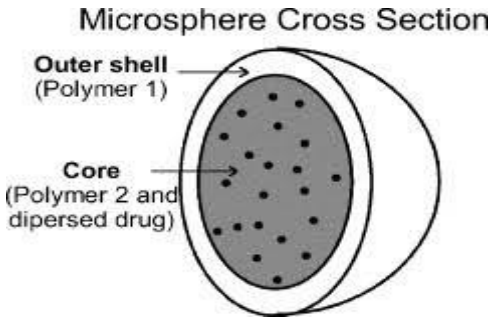


Fig. 1: Microsphere cross section.

Advantages of Microspheres

- Decrease of the size contributes to an increasing the surface area and can increase the potency of the poorly soluble material.
- Providing a steady quantity of medications in the body that can improve patent compliance;
- Drug packaging with polymers prevents the drug avoid enzymatic cleavage while making it suitable for drug method delivery system.
- Less duration of dosing contributes to higher patient compliance.
- Effective usage of medications can enhance bioavailability, and decrease harmful effects occurrence or severity.
- Controlled release delivery degradable microspheres are being used to regulate release of drug prices while also reducing toxicity, and reducing the discomfort of repeated injection.

Disadvantages of Microspheres

- The changed releases from the formulations.
- The release rate of the regulated dose process of release which differ from a number of Factors like diet and transfer levels through gut.
- Variations in rate of discharge from one dosage to the next.
- Controlled release formulations typically have a higher dose load and so any lack of quality of the release properties of the drug substance can contribute to
- Potentially dangerous.
- These dosing types must not be broken or chewed.

Materials used in the microsphere formulation

In the formulation of microsphere mainly used a polymers, they are classified as follows. ➢ Synthetic Polymers ➢ Natural polymers.

Synthetic polymers are divided into two types

a) Non-biodegradable polymers Example- Poly methyl methacrylate (PMMA), Acrolein Glycidyl methacrylate, Epoxy polymers

b) Biodegradable polymers Example- Lactides, Glycolides and their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.

Natural polymers

They are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. They are also used a protein like Albumin, Gelatin, and Collagen, Carbohydrates like Agarose, Carrageenan, Chitosan, Starch and also Chemically changed carbohydrates used like Poly dextran, Poly starch.

MATERIALS AND METHODS

MATERIALS

Empagliflozin were obtained as pure sample from Hetero Labs, HYD, as gift samples along with their analytical reports. Sodium alginate, Ethyl cellulose, Dichloromethane, Span 20 was obtained from Synpharma Research Labs, HYD. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

METHODOLOGY

Preformulation studies

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physic-chemical parameters, invitro release studies and stability studies.

Methods of API characterization

Physical properties

The color odor, tasteof the drug was recorded using descriptive terminology.

Solubility studies

Solubility study of Empagliflozin was performed in water and organic solvents.

Determination of melting point

Melting point of Empagliflozin was determined by capillary method.

Preparation of standard curve of Empagliflozin

Empagliflozin was analyzed using UV/visible spectrophotometer, using a solution prepared in 6.8 pH buffer at 225 nm.

Preparation of 6.8 Phosphate buffer

28.80 gm of Disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in 1000 ml of water.

Preparation of standard solution of Empagliflozin

Stock solution – I

Accurately weighed 10 mg of Empagliflozin was placed in a 10 ml volumetric flask. The volume was made up to 10 ml using water to give 1000 mcg/ml solution.

Stock solution -II

Fromstock solution I 1ml aliquote was taken and placed in a 10 ml volumetric flask and diluted with water to 10ml to get 100mcg/ml.

Stock solution-III

From *stock solution -II*, a 1ml of aliquote was made up to 10ml to get 10mcg/ml.

Similar dilutions were prepared from *stock solution -I* in different media like pH 6.8 buffer solutions.

Determination of absorption maxima (λ_{max}) for Empagliflozin

A 10mcg/ml standard solution of Empagliflozin was scanned on a double beam spectrophotometer against respective media blanks. An absorption maximum (λ_{max}) of 225nm was obtained for all solutions and was selected to prepare standard curve.

Preparation of standard curve for Empagliflozin

Standard curves for Empagliflozin were obtained in 6.8 phosphate buffer. Aliquots of 1, 2, 3, 4 and 5 ml of Empagliflozin standard solution of 100mcg/ml (*stock solution-II*) was taken and diluted to obtain concentrations from 10 mcg/ml with appropriate media. The absorbances of solutions were determined at 225nm against respective media as blank. The experiment was repeated six times for each buffer and a calibration curve was determined from the mean.



Fig. 2: UV Spectrophotometer.

Fourier transform infrared spectroscopy studies

Drug and drug-polymer compatibility research identification procedure: The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm-1). No peaks are observed which interfere with the main drug peaks. The following spectrum and table show IR spectrum for drug and polymer and the wave number of characteristic bands for the same.

Formulation table

Table 1: Composition of Microspheres.

F. code	Drug(mg)	Sodium alginate (mg)	Ethyl cellulose (mg)	Dichloromethane (ml)	Span 20 (w/v)
F1	100	100	-	10	1%
F2	100	200	-	10	1%
F3	100	300	-	10	1%
F4	100	400	-	10	1%
F5	100	-	100	10	1%
F6	100	-	200	10	1%
F7	100	-	300	10	1%
F8	100	-	400	10	1%

Procedure

- Dissolve Empagliflozin and polymers in dichloromethane.
- Add the organic phase slowly into an aqueous phase containing 1% Span 20, under continuous stirring (using magnetic stirrer or homogenizer).
- Stir the mixture for 2–3 hours to allow complete evaporation of dichloromethane.
- Collect the formed microspheres by filtration or centrifugation.
- Wash microspheres with distilled water.
- Dry them at room temperature or in a desiccator.

Evaluation of microspheres

Particle Size and Zeta Potential

The particle size of the formulation was determined by photo correlation spectroscopy with a zeta master (Malvern Instruments, UK) equipped with the Malvern PCS software. Every sample was diluted with distilled water. The surface charge (Zeta potential) was determined by measuring the electrophoretic mobility of the nanoparticles using a Malvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with distilled water.[39]

SEM analysis

The morphology of microspheres was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminum stubs and the surface was coated with a layer of gold particles using a sputter coater. The shape of the NPs was determined by scanning electron microscopy (SEM) (XL30, Philips, the Netherlands) at 15 kV and 750 mA.[40]

Percentage Yield

To prepared sustained release microsphere of all batches accurately weight. The measured weight of prepared microspheres was divided by total amount of all excipient and drug used in preparation of oral microspheres, which give the total percentage yield of total microspheres. It was calculated by following equation;[41]

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100$$

Drug Entrapment Efficiency

Entrapment efficiency of oral microspores was evaluated by deriving percent drug entrapment. the drug content of drug loaded oral microsphere was determine by dispersing 10 mg of oral microspheres in 10 ml ethanol followed by agitation with of magnetic stirrer for about 30 min to extract the drug and dissolved completely. After filtration though paper the 1 ml of filtrate is pipette out and diluted up to 10 ml volumetric flask. Drug concentration in ethanol phase was recorded by taking absorbance of this solution. The drug concentration was calculated. Thus, the total drug entrapped in total yield of microspheres from the procedure was calculated. It is express in percentage it is called as % drug entrapment. The amount of drug loaded and entrapped in oral microsphere was calculated by following formula.[42]

% Drug Entrapment = Amount of drug actually present / Theoretical drug loaded expected × 100

In-Vitro Dissolution Study

The in-vitro dissolution study was performed using the USP Type II (paddle) dissolution apparatus, depending on the dosage form. The dissolution medium, typically 900 mL of phosphate buffer (pH 6.8) or other suitable media, was maintained at 37 ± 0.5°C throughout the study. The dosage form was placed in the dissolution vessel, and the paddle was rotated at a predetermined speed, usually 50–100 rpm. Samples of 5–10 mL were withdrawn at predetermined time intervals and immediately replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were filtered through a 0.45 µm membrane filter, and the drug content was analyzed using a UV-Visible spectrophotometer the drug's characteristic wavelength. The percentage of drug released was calculated using the measured concentration, and a dissolution profile was plotted as percentage drug release versus time. All experiments were conducted in triplicate to ensure reproducibility, and the data were used to assess the release behavior of the formulation.

Kinetics of drug release studies

Zero order release kinetics

It refers to the process of constant drug release from a drug delivery device independent of the concentration. In its simplest form, zero order release can be represented as

$$Q = Q0 + K0\, t$$

Where Q is the amount of drug released or dissolved,
Q0 is the initial amount of drug in solution (it is usually zero), and K0 is the zero-order release constant. The plot made: cumulative drug release vs. time. Graphical representation of fraction of drug dissolved verses time will be linear. The slope of the curve gives the value of K in zero order release kinetics. This is ideal behavior for a dosage form and leads to minimum fluctuations in drug plasma levels. This is expressed mainly by osmotic pump systems and also transdermal systems, matrix tablets with low soluble drugs and coated forms.

First order release kinetics

The first order Equation describes the release from system where release rate is concentration dependent, expressed by the equation:

$$dC / dt = - Kt$$

Where
K is first order rate constant expressed in units of time-1.
This equation can be expressed as: $\text{Log } Ct = \text{Log } C0 - k\, t / 2.303$
Where,
C0 is the initial concentration of drug and
Ct is the concentration of drug in solution at time t.

The equation predicts a first order dependence on the concentration gradient (Co - Ct) between the static liquid layer next to the solid surface and the bulk liquid. The plot made: log cumulative of % drug remaining vs. time which would yield a straight line with a slope of – K/2.303.

Higuchi Model

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1963 this model is applicable to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices Model expression is given by the equation:

$$Q = A [D (2C - Cs) Cs t] 1/2$$

Where

Q is the amount of drug released in time t per unit area A,

C is the drug initial concentration,

Cs is the drug solubility in the media and D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix.

Simplified Higuchi model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Equation.

$$Q = KH\ t1/2$$

The data obtained were plotted as cumulative percentage drug release versus square root of time. The slope of the plot gives the Higuchi dissolution constant KH.

Korsmeyer - Peppas Model

To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer – Peppas model

$$Mt / M\alpha = K\ tn$$

Where

Mt/Mα is fraction of drug released at time t, k is the rate constant (having units of tn) incorporating structural and geometric characteristics of the delivery system. n is the release exponent indicative of the mechanism of transport of drug through the polymer. The n value is used to characterize different release mechanisms.

Stability studies

Once the delivery system was developed, the practical utility of the formulation depends on the maintenance of the therapeutic efficacy throughout the shelf-life under different storage conditions. Various Invitro characterization parameters (physical appearance, entrapment efficacy, and drug release) of the microspheres were assessed after storage of the best formulations for 3 and 6 months at 40±2^{o}C/ 75±5% RH according to ICH guidelines, and results were compared with those obtained before storage.

RESULTS AND DISCUSSION

Preformulation studies

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physic-chemical parameters, in-vitro release studies and stability studies.

API Evaluation

a) Organoleptic evaluation

Table 2: Organoleptic properties of Empagliflozin.

Properties	Results
Description	Crystalline powder
Taste	Tasteless
Odor	Odorless
Color	WwWhite to off-white crystalline powder

b) Solubility

Freely soluble in dimethyl sulfoxide (DMSO), Ethanol and methanol, slightly soluble in water.

Table 3: Solubility of Empagliflozin.

Vehicle	Avg. Solubility* (mg/ml)
DMSO	99
Methanol	95
Ethanol	85
Water	42

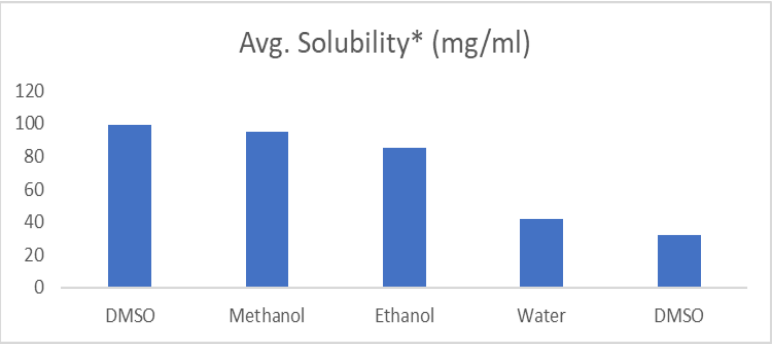


Fig. 16: Solubility of Empagliflozin.

Determination of melting point

Melting point of Empagliflozin was found in the range of 110-114^{0}c, which complied with the standard, indicating purity of the drug sample.

Determination of λ max of Empagliflozin

From the UV spectrophotometric analysis, it was concluded that the drug, Empagliflozin showed a λ max at225nm which was similar with the reported λ max of Empagliflozin (USP). Therefore, the observed λ max was used for further experimental work to analyze the test samples.

Standard graph of Empagliflozin in pH 6.8 buffer

The solution obeyed Beer- Lambert's law over a concentration range of 1-5 µg/ml with a regression co-efficient of 0.996. This standard curve was used further to estimate Empagliflozin in the in vitro samples.

Table 6: Data for standard graph of Empagliflozin in Phosphate buffer pH 6.8.

Concentration (µg/ml)	Absorbance in pH6.8 buffer
0	0
1	0.135
2	0.324
3	0.519
4	0.720
5	0.912

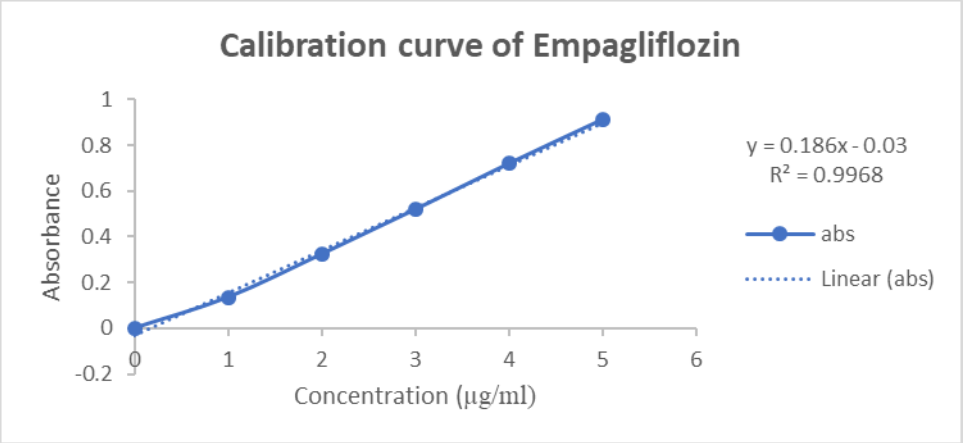


Fig. 18: Standard graph of Empagliflozin in pH 6.8 buffer.

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected polymer and other excipients was evaluate dusing FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymers and other chemicals.

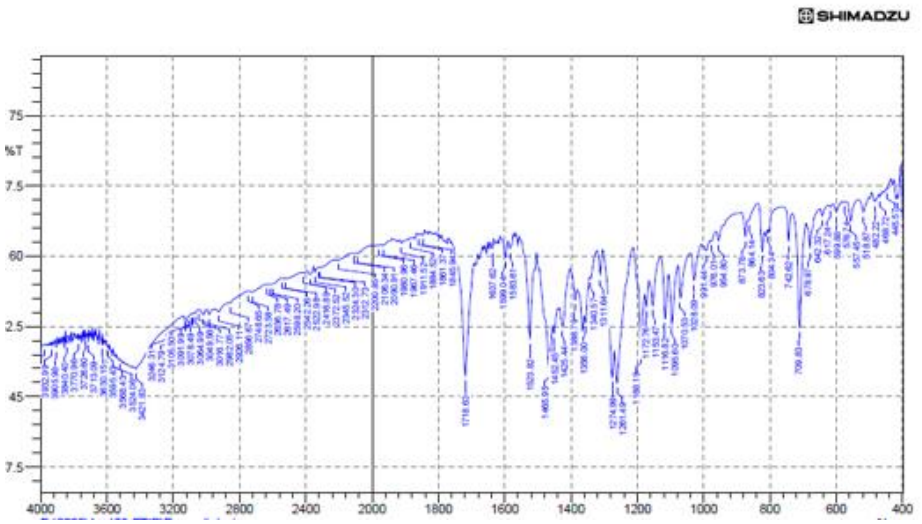


Fig. 19: FTIR Spectra of Empagliflozin.

Table-7: Characteristic Peaks for Empagliflozin.

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3600-2800	3124.79
2	C–O stretching	1400-1000	1311.04
3	C-H stretching	2800-1800	2723.56
4	C=O stretching	1800-1600	1718.63
5	C–H bending	1000-600	954.80

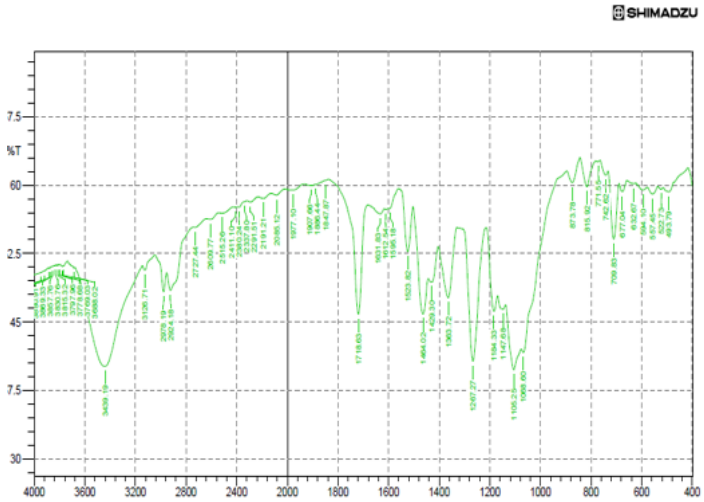


Fig. 20: FTIR Studies of Optimized formulation.

Table 8: Characteristic Peaks for Optimized formulation.

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3200	3439.19
2	O–Hbending	1800-1400	1718.63
3	C-H stretching	3200-2800	2979.19
4	C-H bending	1600-1200	1404.02
5	C-O stretching	1200-600	1105.25

Characterization of microspheres

Particle size analysis

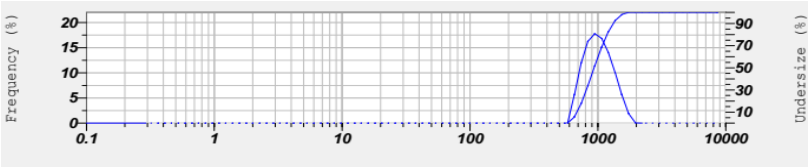


Fig. 21: Particle size analysis of Optimized formulation.

Table 9: Particle size of Different formulations of Microspheres.

Formulation code	Mean particle size* (µm)
F1	759
F2	824
F3	869
F4	789
F5	836
F6	849
F7	750
F8	746

Zeta potential

Table 10: Zeta potential for different formulation.

Formulation	Zeta potential (-mV)
F1	-25
F2	-35
F3	-36
F4	-27
F5	-22
F6	-20
F7	-28
F8	-24

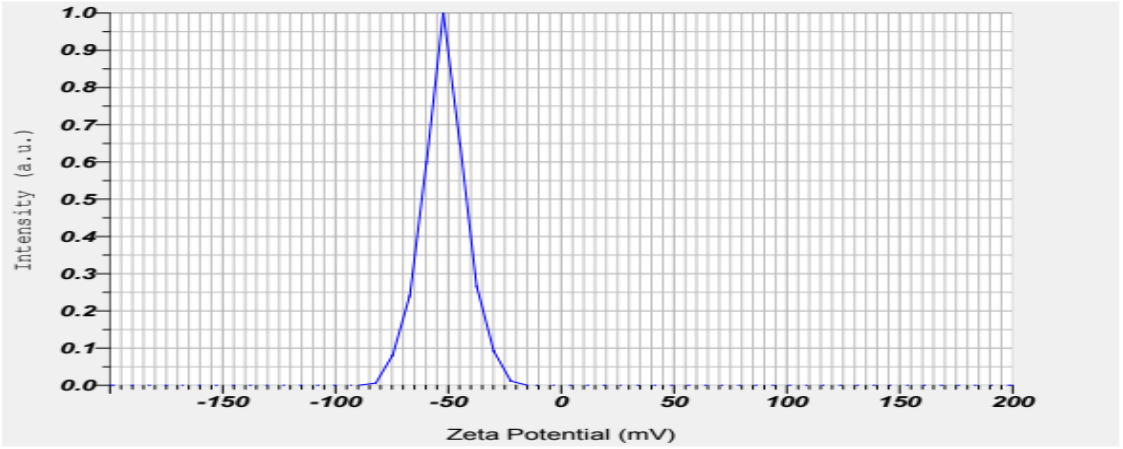


Fig. 22: Zeta potential of optimized formulation.

Percentage Yield

Table 11: Percentage yield for different formulation.

Formulation	Percent Yield*(%)
F1	72.59
F2	82.35
F3	76.32
F4	83.25
F5	79.80
F6	85.37
F7	76.36
F8	85.59

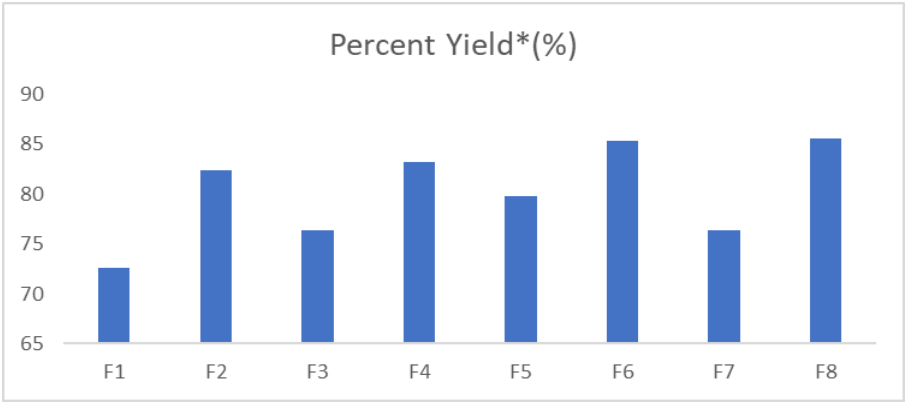


Fig. 23: Percentage yield for different formulation.

Scanning Electronic Microscopy

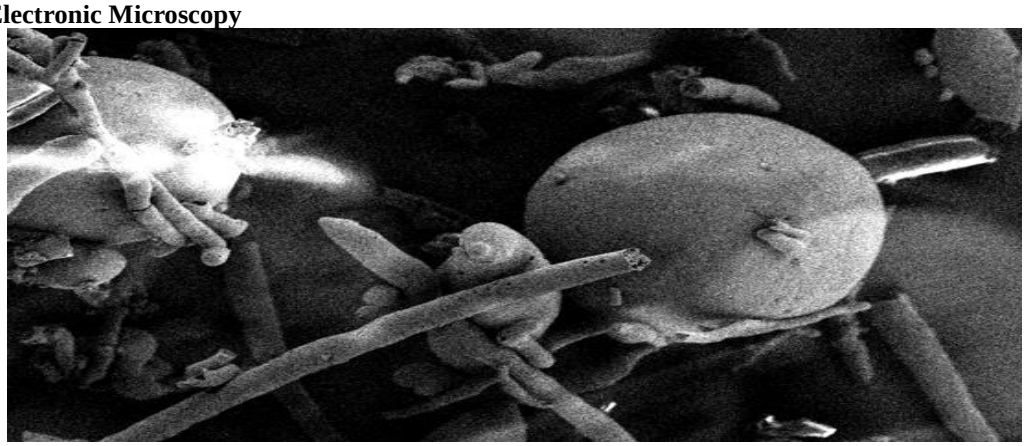


Fig. 24: SEM Analysis of Optimized formulation.

Drug Entrapment efficiency

Table 12: Drug entrapment for different formulation.

Formulation	Drug Entrapment (% w/w)
F1	76.39
F2	82.19
F3	79.80
F4	82.34
F5	85.36
F6	84.97
F7	90.25
F8	92.53

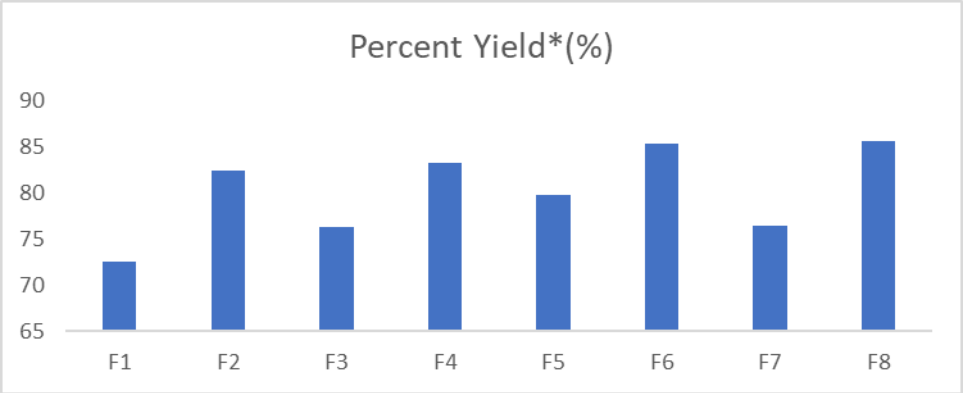


Fig. 25: Drug entrapment for different formulation.

***In*-vitro Drug release study**

Table 13: Comparative *In-Vitro* Drug Release Profile for (F1-F8) Formulation.

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	17.32	18.55	16.42	17.12	18.21	16.25	17.43	18.25
2	28.10	27.96	27.82	25.63	34.75	25.63	25.27	29.81
3	40.38	41.37	42.51	42.18	45.20	43.58	41.21	45.58
4	54.69	55.86	54.10	55.98	55.28	56.72	52.39	58.97
5	68.12	69.76	65.28	66.34	67.45	69.16	65.33	68.98
6	73.69	75.83	73.69	74.50	77.20	76.83	74.59	78.42
7	82.16	81.37	80.22	81.42	82.19	82.56	80.12	83.56
8	94.55	94.68	96.28	95.50	96.35	94.72	95.69	98.22

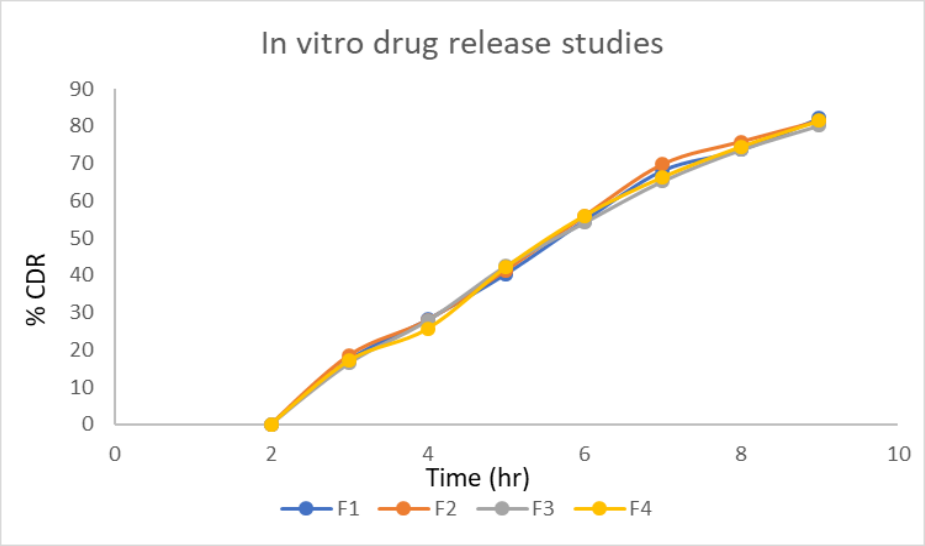


Fig. 26: Comparative In-Vitro Drug Release Profile Of(F1-F5) formulation.

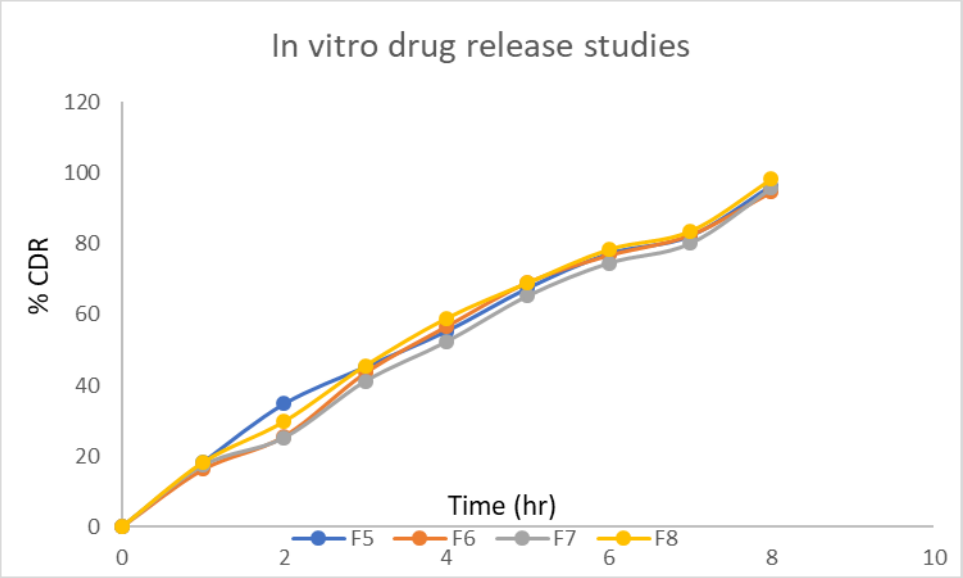


Fig. 27: Comparative In-Vitro Drug Release Profile Of(F5-F8) formulation.

Drug release kinetics

Table 14: Drug Release Kinetics of Formulation F8.

Time (hrs)	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
1	18.25	1.26126287	0	1	81.75	1.9124878
2	29.81	1.47436198	0.30103	1.414214	70.19	1.8462752
3	45.58	1.65877432	0.477121	1.732051	54.42	1.7357585
4	58.97	1.77063113	0.60206	2	41.03	1.6131015
5	68.98	1.83872319	0.69897	2.236068	31.02	1.4916418
6	78.42	1.89442684	0.778151	2.44949	21.58	1.3340514
7	83.56	1.92199843	0.845098	2.645751	16.44	1.2159018
8	98.22	1.99219993	0.90309	2.828427	1.78	0.25042

Zero order kinetics

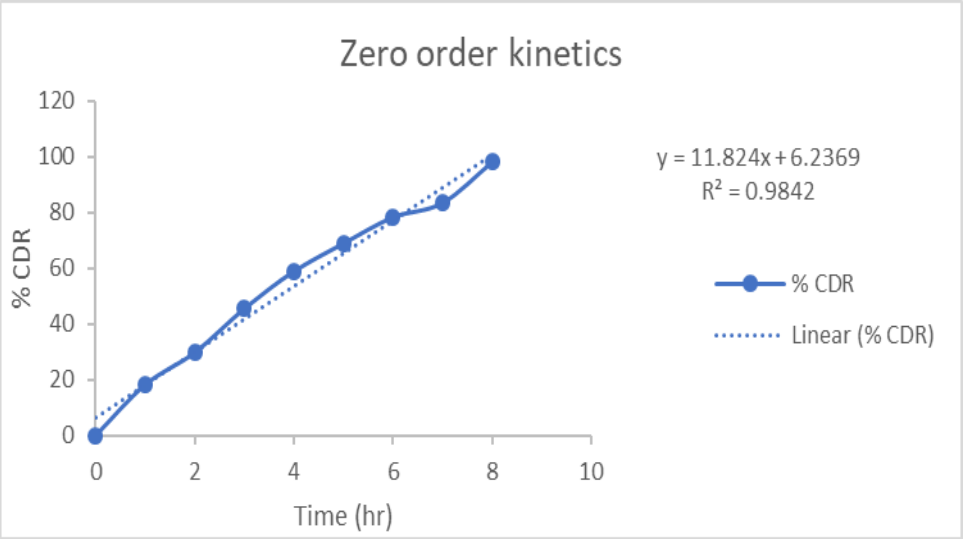


Fig. 28: Zero order kinetics of optimized formulation.

First order kinetics

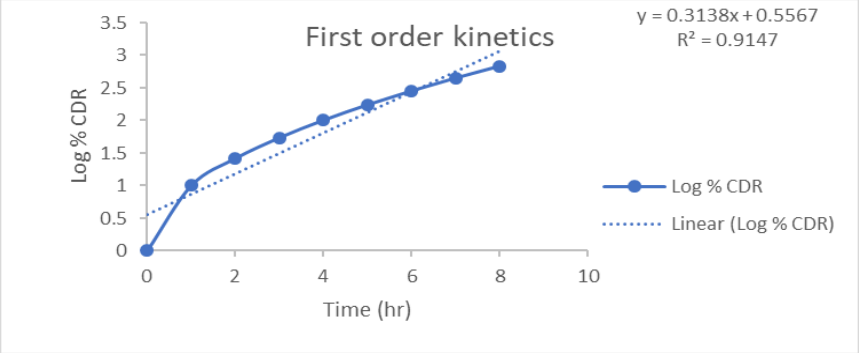


Fig. 29: First order kinetics optimized formulation.

Higuchi model

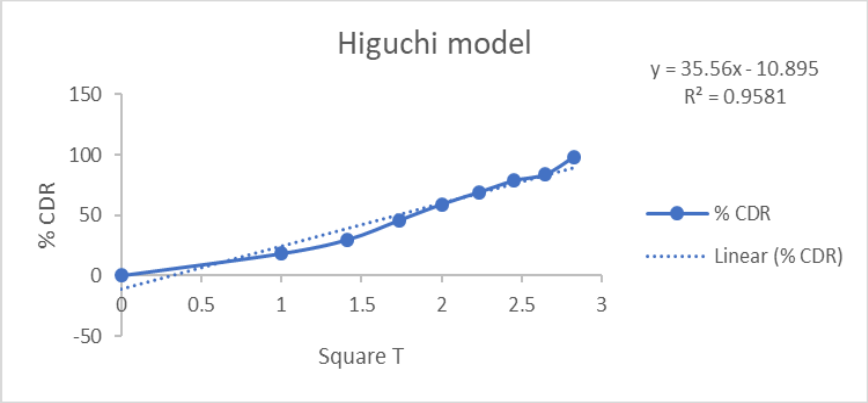


Fig. 30: Higuchi modeloptimized formulation.

Korsmeyer peppas

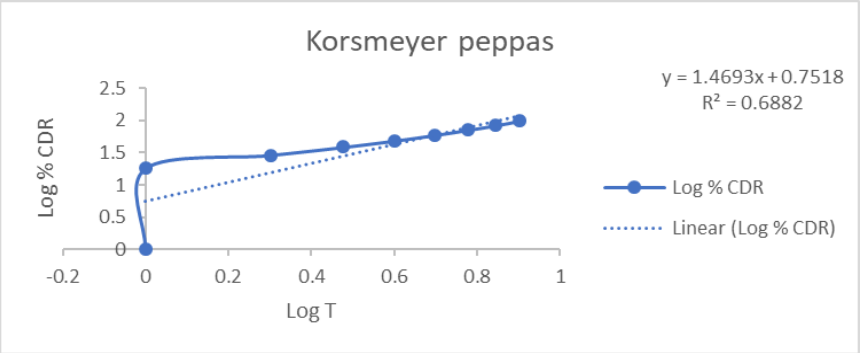


Fig. 31: Korsmeyer peppasoptimized formulation.

Table 18: Regression equations of Empagliflozin microspheres.

F. no	In vitro release in phosphate buffer P^H 7.4 Regression values			
	Zero order	First order	Higuchi Plot	Korsmeyer peppas
F8	0.984	0.914	0.958	0.918

Stability Study

Table 15: Results of stability studies of optimized formulation F-8.

S.NO	Time in days	Physical changes	Mean % drug release		
			Empagliflozin		
			25^0C/60%	30^0C/75%	40^0C/75%
1	1	No Change	98.22	98.22	98.22
2	30	No Change	97.58	97.1	97.22
3	60	No Change	96.38	96.57	96.35
4	90	No Change	95.51	95.20	95.10

DISCUSSION

Particle Size Analysis

The particle size of the prepared Empagliflozin microspheres was found to range from 746 µm to 869 µm, indicating successful formation of microspheres with relatively uniform size distribution. The optimized formulation (F8) exhibited a mean particle size of 746 µm, which was among the smallest of all formulations. The reduction in particle size of F8 may be attributed to the optimized polymer-to-drug ratio and efficient emulsification conditions during preparation. Smaller particle size provides a larger surface area, which enhances dissolution and contributes to improved drug release. The particle size obtained is suitable for oral sustained-release microsphere formulations and demonstrates effective process optimization.

Zeta Potential

The zeta potential values of the microspheres ranged from −20 mV to −36 mV. The optimized formulation (F8) showed a zeta potential of −24 mV, indicating moderate electrostatic stability. Negative zeta potential values suggest sufficient surface charge to minimize particle aggregation during storage. Although F8 did not possess the highest negative value, its zeta potential was adequate to maintain physical stability while ensuring good dispersion characteristics.

Percentage Yield

The percentage yield of all formulations varied between 72.59% and 85.59%. The optimized formulation F8 exhibited the highest production yield (85.59%), indicating minimal material loss during the preparation process. The improved yield may be due to efficient polymer encapsulation and optimized process parameters, which reduced adhesion of microspheres to the equipment and minimized drug wastage. High percentage yield demonstrates the reproducibility and suitability of the preparation method for large-scale production.

Scanning Electron Microscopy (SEM)

SEM analysis of the optimized formulation (F8) revealed that the microspheres were spherical, discrete, and possessed a smooth surface with minimal surface irregularities. The absence of cracks or pores indicates uniform polymer coating around the drug particles, which contributes to sustained drug release. The spherical morphology also confirms successful microsphere formation and suggests good mechanical stability of the prepared formulation.

Drug Entrapment Efficiency

Drug entrapment efficiency of the formulations ranged from 76.39% to 92.53%. Among all formulations, F8 exhibited the highest entrapment efficiency (92.53%), indicating efficient incorporation of Empagliflozin within the polymeric matrix. The high entrapment

efficiency may be attributed to the optimized polymer concentration, which effectively reduced drug diffusion into the external phase during preparation. Efficient drug encapsulation is essential for achieving sustained drug release and improving therapeutic efficacy.

In-vitro Drug Release Study

The cumulative drug release study demonstrated sustained release behavior for all formulations over an 8-hour period. The optimized formulation F8 released 98.22% of the drug at the end of 8 hours, which was higher than the remaining formulations. The release profile indicated an initial controlled release followed by gradual and sustained drug diffusion from the polymeric matrix. The optimized polymer concentration in F8 successfully controlled drug release while ensuring nearly complete release within the desired time. Such a release profile is beneficial for maintaining therapeutic drug levels and reducing dosing frequency.

Drug Release Kinetics

The release kinetics of the optimized formulation F8 were analyzed using various mathematical models. The regression coefficients obtained were:

Zero-order model ($R^2 = 0.984$)
First-order model ($R^2 = 0.914$)
Higuchi model ($R^2 = 0.958$)
Korsmeyer–Peppas model ($R^2 = 0.918$)

Among these models, the Zero-order kinetic model showed the highest regression coefficient ($R^2 = 0.984$), indicating that the drug release from F8 followed zero-order kinetics. This suggests that Empagliflozin was released at a nearly constant rate throughout the study period, which is desirable for sustained-release formulations. The comparatively high Higuchi regression value also indicates that diffusion through the polymer matrix contributed significantly to the release mechanism.

Stability Studies

The stability study of the optimized formulation (F8) was conducted under ICH-recommended storage conditions for 90 days. No significant physical changes such as discoloration, aggregation, or deformation were observed throughout the study. The cumulative drug release decreased only slightly from 98.22% initially to 95.51%, 95.20%, and 95.10% under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH, respectively. The minor reduction in drug release indicates excellent stability of the formulation under different environmental conditions. These findings demonstrate that the optimized microspheres maintained their structural integrity and drug release characteristics throughout the storage period, confirming their suitability for pharmaceutical application.

CONCLUSION

The present investigation successfully demonstrated the formulation and evaluation of Empagliflozin microspheres by the solvent evaporation technique for sustained oral drug delivery. The prepared microspheres exhibited satisfactory physicochemical characteristics, high production yield, excellent drug entrapment, desirable particle morphology, and controlled drug release. Among all the formulations, F8 was identified as the optimized formulation owing to its highest drug entrapment efficiency (92.53%), maximum percentage yield (85.59%), smallest particle size (746 µm), and highest cumulative drug release (98.22% in 8 hours). The optimized formulation followed Zero-order release kinetics, indicating a nearly constant drug release pattern suitable for sustained-release therapy. Furthermore, the formulation remained physically and chemically stable during the 90-day stability study, demonstrating its robustness and storage stability. Overall, the developed Empagliflozin microspheres represent a promising sustained-release drug delivery system that may improve therapeutic efficacy, reduce dosing frequency, enhance patient compliance, and provide better management of Type 2 Diabetes Mellitus.

REFERENCES

1. Allen, L. V., Popovich, N. G., & Ansel, H. C. (2011). Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (9th ed.). Lippincott Williams & Wilkins.
2. Banker, G. S., & Rhodes, C. T. (2013). Modern Pharmaceutics (4th ed.). CRC Press.
3. Chien, Y. W. (2005). Novel Drug Delivery Systems (2nd ed.). Marcel Dekker.
4. Jain, N. K. (2008). Controlled and Novel Drug Delivery. CBS Publishers & Distributors.
5. Kreuter, J. (1994). Colloidal Drug Delivery Systems. Marcel Dekker.
6. Langer, R. Drug delivery and targeting. Nature, 1998; 392: 5–10. https://doi.org/10.1038/32000
7. Park, K. (2010). Controlled Drug Delivery: Challenges and Strategies (2nd ed.). American Chemical Society.
8. Robinson, J. R., & Lee, V. H. L. Controlled Drug Delivery: Fundamentals and Applications (2nd ed.). CRC Press, 2005.
9. Sinha, V. R., &Trehan, A. Biodegradable microspheres for parenteral delivery. Critical Reviews in Therapeutic Drug Carrier Systems, 2003; 20(1): 1–20. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v20.i1.10
10. Verma, R., & Stella, V. J. Drug delivery: Controlled and novel drug delivery. Annual Review of Pharmacology and Toxicology, 2000; 40: 455–484. https://doi.org/10.1146/annurev.pharmtox.40.1.455
11. Vyas, S. P., & Khar, R. K. (2002). Targeted and Controlled Drug Delivery: Novel Carrier Systems. CBS Publishers & Distributors.
12. Shaik shabbeer, Aruri madhavi, Santhosh Illendula. Formulation and in vitro evaluation of timolol Maleate of sustained release matrix tablets by using

different polymers, World journal of pharmacy and pharmaceutical sciences, 2024; 13(06): 511-524.
13. Shaik shabbeer, K Anjaneyulu, Santhosh Illendula, Nanoparticle based drug delivery system for sulfadiazine drug along with herbal extract, International research journal of education and technology, 2024; 06(05): 307-326.
14. Shaik shabbeer, G. Uma Maheshwari, Santhosh Illendula, Formulation and evaluation of Idarubicin, International Journal of Pharmacy and Biological Sciences-IJPBS, 2022; 12(3): 127-141
15. Whitehead, L., et al. Microencapsulation and drug delivery. Journal of Controlled Release, 2005; 102(2): 145–155. https://doi.org/10.1016/j.jconrel.2004.09.018
16. Zhang, Y., & Chan, H.F. Advances in micro- and nano-particles for drug delivery. Advanced Drug Delivery Reviews, 2013; 65(1): 3–12.
17. Vasir JK. Tambwekar K. Garg S. Bioadhesive microsphere as a controlled drug delivery system. International Journal of Pharmaceutics. 2003; 255(1-2): 13-32.
18. Sarika, et al. Oral drug delivery is the most preferred and expedient option as the oral route provides greatest active surface area among all drug delivery system for administration of various drugs. *Journal of Pharmaceutical Research*, 2019; 12(3): 45–53.
19. Satbir Singh, et al. Microspheres in drug delivery: Recent developments in innovative dosage forms. *International Journal of Pharmaceutical Sciences*, 2024; 16(2): 101–115.
20. Santhosh Illendula, Peddaboina Shiva prasad., Analytical Method Development and Validation of RP-HPLC for The Quantitative Determination of Baricitinib in Pure Substances and Marketed Formulation. International Journal of Pharmacy and Biological Sciences-IJPBS™, 2022; 12(3): 108-114. DOI: https://doi.org/10.21276/ijpbs.2022.12.3.15
21. Santhosh Illendula et al., Method Development and Validation of Afatinib in Bulk and Pharmaceutical Dosage Form by UV-Spectroscopic Method, Indo Am. J. P. Sci., 2018; 05(03).
22. Patrick B., et al. Microencapsulation and solvent evaporation techniques for biodegradable polymer-based microspheres: Challenges in protein and peptide encapsulation. *Journal of Controlled Release*, 2023; 355: 12–30.
23. Patibandla Jahnavi, et al. Formulation and evaluation of sustained release microspheres for anti-diabetic drugs. *Journal of Drug Delivery Science and Technology*, 2025; 78: 104–118.
24. Rajarao Chinta, et al. Development and optimization of empagliflozin and metformin hydrochloride bilayer tablets. *Research Journal of Pharmacy and Technology*, 2021; 14(7): 3476–3485.
25. Neeraja Podichety, et al. Formulation and evaluation of empagliflozin microspheres using solvent evaporation technique. *International Journal of Pharmaceutical Research*, 2023; 15(1): 205–218.