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STIMULI-RESPONSIVE NANOSPONGE SYSTEM FOR ANTI DIABETIC THERAPHY

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ABSTRACT

The present study was undertaken to develop and evaluate a pH-responsive nanosponge system of Metformin HCl for controlled and site-specific drug delivery. Nanosponges were prepared by the emulsion solvent diffusion method using Ethyl Cellulose as the polymer and Polyvinyl Alcohol (PVA) as the stabilizer. The prepared nanosponges were subsequently modified with Polyacrylic Acid (PAA) to impart pH-responsive drug-release characteristics. Different formulations (F1–F6) were prepared by varying the polymer concentration and evaluated for production yield, drug entrapment efficiency, drug content, particle size, FT-IR, DSC, SEM, and in-vitro drug release. The production yield of the formulations ranged from 79.81% to 84.25%, while drug entrapment efficiency ranged from 78.15% to 92.89%. The particle size was found to be in the range of 303–680 nm. FT-IR studies indicated the retention of characteristic functional groups of Metformin HCl and polymers without major chemical interaction, confirming drug–excipient compatibility. SEM analysis demonstrated the porous nature of the prepared nanosponges. The optimized formulation exhibited pH-dependent drug release, showing relatively low release at acidic pH 1.2 and 4.4, with cumulative drug release of 28.30% and 32.96%, respectively, after 24 h. In contrast, considerably higher drug release of 76.24% was observed at pH 6.8 after 24 h, indicating enhanced release under intestinal pH conditions. The optimized nanosponge formulation demonstrated sustained and pH-responsive drug release and followed predominantly zero-order kinetics. The findings suggest that PAA-coated Metformin HCl nanosponges may provide a promising approach for controlled oral drug delivery with enhanced intestinal drug release.

KEYWORDS: Metformin HCl, Nanosponges, pH-responsive drug delivery, Polyacrylic Acid, Ethyl Cellulose, controlled release.

INTRODUCTION

Nanosponge is a modern category of material and it is made up of tiny particles with a narrow cavity of few nanometers. These narrow cavities can be filled with various types of substances these tiny particles are having capability due to which it is able to carry both hydrophilic and lipophilic drug substances. Release the drug at specific target site instead of circulate through the body it will more effective for particular given dosage. The invention of nanosponges has become significant step towards overcoming the complexity associated with the newly developing systems. The small size and porous nature of nanosponges can bind poorly water-soluble drugs within the matrix and improve their solubility and bioavailability. Nanosponges are able to entrap both hydrophilic as well as lipophilic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility. Nanosponge obtained by using suitable cross-linking agent also by different organic and inorganic materials. The stability of these formulations over a wide range of pH in GI fluids and stable over 130 °C compatible with most vehicles and ingredients. Reducing dosing frequency and increase patient compliance and comfort. This drug delivery system having entrap wide variety of ingredients and reducing side effects, improve stability, increased elegance and formulation flexibility. The effort to improve dissolution and solubility of poorly and practically water insoluble drugs remains one of the most challenging tasks in drug development. Several methods have been introduced to increase dissolution rate and thereby oral absorption and bioavailability of such drugs. Among various approaches, Nanosponges has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability. The nanosponges can overcome some of the shortcomings of the conventional dosage forms. Metformin Hcl is one of the second-generation sulphonyl urea, antidiabetic drug which stimulates insulin release. It is used for the treatment of non-insulin-dependent diabetes mellitus. Metformin Hcl is classified under class III according to biopharmaceutical classification system (BCS). The drug shows low, pH dependent solubility. In acidic and neutral aqueous media, Metformin Hcl exhibits very poor solubility. This poor solubility may cause poor dissolution and unpredicted bioavailability. Preparation of nanosponges of Metformin Hcl to improve the dissolution rate of Metformin Hcl and subsequently its bioavailability. The main objective of the study was to increase the amount of dissolved drug molecules at the absorption site by increasing the dissolution rate, since for class III drugs like Metformin Hcl, *in vivo* dissolution rate is rate-limiting step in drug absorption. nanosponges were selected as the method of choice since it would be easier in subsequent formulating. The nanosponges were prepared at various drug-to carrier weight ratios by emulsion solvent diffusion method.

Stimuli-Responsive Nanosponges

Stimuli-responsive nanosponges are smart drug delivery systems that respond to specific changes in their surrounding environment. These changes act as a stimulus and control the release of the drug from the nanosponge. Common stimuli include pH, temperature, enzymes, light, redox conditions and magnetic fields.

pH-Responsive Nanosponges

pH-responsive nanosponges are a type of stimuli-responsive nanosponge that release the drug in response to changes in pH. They are prepared using pH-sensitive polymers containing ionizable functional groups such as carboxyl (-COOH) or amino ($-NH_2$) groups.

They can take advantage of the differences in pH between different parts of the body, such as the stomach, intestine, tissues and certain disease environments, to achieve controlled drug release.

MATERIAL AND METHODS

Material

Metformin Hcl was provided by Yarrow chem product India. Dichloromethane (DCM), Polyvinyl Alcohol (PVA) was provided by research-Lab Fine Chem Industries Mumbai,India, Ethyl cellulose was provided by Research-Lab Fine Chem Industries Mumbai, India.

Methods

Metformin Hcl nanosponges were prepared by emulsion solvent diffusion method. In this method, two phases used are aqueous and organic. Aqueous phase consists of polyvinyl alcohol and organic phase include Metformin Hcl and Ethyl Cellulose. After dissolving Metformin Hcl and Ethyl cellulose to suitable organic solvent. This phase added slowly to the aqueous phase and stirred for two or more hours and then nanosponges are collected by filtration, washed, and then dried in air at room temperature or in vacuum oven 40 °C for 24 h.

The nanosponges are first prepared and collected. A dilute PAA solution (0.1–0.5% w/v in water) is then prepared, and the nanosponges are redispersed in the PAA solution. The dispersion is stirred gently for several hours to allow PAA to adsorb onto the particle surface. If a permanent coating is required, an appropriate cross-linking or coupling method compatible with the formulation is used. The PAA-coated nanosponges are then separated by centrifugation and washed with distilled water to remove unbound PAA. Finally, the coated nanosponges are freeze-dried to obtain the dried PAA-coated nanosponges.

Table 1: Formulation of Metformin Hcl loaded nanosponges.

Formulation code	Metformin HCL (mg)	Ethyl Cellulose (mg)	PVA (% W/V)	Dichloro Methane (ml)	Polyacrylic Acid	RPM	Strring Time (hr)
F1	100	200	0.5	10	20	1500	2
F2	100	250	0.75	10	40	1500	2
F3	100	300	1.0	10	60	1500	2
F4	100	350	1.25	10	80	1500	2
F5	100	400	1.5	10	100	1500	2
F6	100	450	2.0	10	120	1500	2

Pre-formulation studies of pure drug

Construction of calibration curve

Stock I

Accurately weighed 10 mg of Metformin Hcl was dissolved the insufficient amount of phosphate buffer 6.8 and volume was made to 10 ml with it. (conc 1000µg/ml)

Stock II

From stock-I 1 ml sample is withdrawn by pippete and diluted to 10 ml of by using phosphate buffer 6.8(100µg/ml)

Stock III

From stock II Working standard solution of strengths0,2,4,6,8,10(µg/ml) were made from the stock solution by appropriate dilution.

Drug-excipient compatibility studies

The drug and excipient compatibility studies were carried out by Fourier transform-infrared spectroscopy (FT-IR). The Potassium Bromide pellets were prepared on KBr press on grounding the solid powder sample with 100 times the quantity of KBr in mortar. The spectra recorded over the wavenumber of 4000 to 400 cm^{-1}.

Evaluation studies of prepared nanosponges

From the results obtained by solubility and dissolution studies, nanosponges which showed better result was selected. For further characterization, nanosponges were performed to access interaction if any between the drug and polymer and also to find out what properties of polymer make them an effective material for solubility and bioavailability enhancement. In present study, the nanosponges of Metformin Hcl with Ethyl Cellulose were characterized by FT-IR, DSC, SEM, *in vitro* drug release study, production yield, entrapment efficiency etc.

Production yield

The production yield (PY) can be determined by calculating the initial weight of raw materials and final weight of nanosponges.

$$\text{Production yield} = \frac{\text{Practical mass of nanosponges}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

The percentage yield of different batches was determined by weighing the nanosponges after drying.

Drug entrapment efficiency

To calculate the entrapment efficiency accurately weighed the quantity of nanosponges (10 mg) with 5 ml of phosphate buffer(6.8) in a volumetric flask was shaken for 1 min using vortex mixer. The volume was made up to 10 ml. Then the solution was filtered and diluted and the concentration of Metformin Hcl was determined spectrophotometrically at 232 nm.

$$\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100$$

Determination of drug content

To study the amount of drug incorporated in the nanosponges, Metformin Hcl was extracted from the nanosponges by dissolving them in 25 ml phosphate buffer (6.8). The resulting solution was filtered through a 0.45-micron membrane filter. The Metformin Hcl content in the methanolic extracts was analyzed spectrophotometrically by using a UV-Visible spectrophotometer (UV Jasco V630) at a wavelength of 232nm, against methanol as blank.

$$\% \text{ drug content} = \left(\frac{Wa}{Wt}\right) \times 100$$

Where, Wa = Actual drug content an; Wt = Theoretical drug content

Determination of particle size

The size of particles is maintained during polymerization for the formation of free-following powders having fine aesthetic attributes. Particle size analysis of loaded and unloaded nanosponges performed by laser light diffractometry or Malvern zeta sizer. The cumulative graph is maintained or plotted as particle size against time to study effect of particle size on drug release.

***In vitro* drug release studies**

In vitro drug release studies were performed in triplicate using USP Paddle method at 50 rpm and 37±0.2˚C in 900 ml of phosphate buffer (pH 6.8). 100 mg of the formulated nanosponges is used for each experiment. Samples were taken at appropriate time intervals for 1 h interval for 10hr. The samples were measured spectrophotometrically at 232 nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume.

Fourier-transform infrared analysis

Fourier-transform infrared (FTIR) spectra of pure Metformin Hcl and pure polymer (Ethyl Cellulose), and nanosponges of drug Metformin Hcl was taken to access interaction if any interaction between drug and polymer in mixtures. The scanned mixture by using an FTIR (shimadzu). The FTIR spectra of mixtures were compared with that of the pure drug and Polymer to assess any change in the principle peaks of spectra of pure drug and polymer.

Differential scanning calorimetry

Differential scanning calorimetric (DSC) studies of pure Metfotmin Hcl, pure polymer (Ethyl Cellulose) and nanosponges of drug Metformin Hcl with Ethyl Cellulose was performed to assess what changes happen during the heat change and thermal behavior of the drug is also determine. The pure drug sample shows sharp endothermic peak at melting point of drug. The samples were kept on DSC reference pan and DSC curves were obtained by differential scanning calorimeter (DSC 60; Shimadzu) at a heating rate of 10 °C/min from 0 to 300 °C in nitrogen atmosphere.

Scanning electron microscopy studies

Scanning electron microscopy was used to analyze particle size and surface topography was operated at 15kV acceleration voltage. A concentrated aqueous suspension was spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with a gold layer 20 nm thick. Photographs were elaborated by an image processing program and individual NP diameters were measured to obtain mean particle size.

Nanosponges that showed the best results in the solubility and dissolution studies were subjected to scanning electron microscopy (SEM) studies to confirm the changes mounting made during the formation of nanosponges. Samples were prepared by powder onto a brass stub using graphite glue and coated with gold under vacuum before use. Images were recorded at the required magnification at an acceleration voltage of 10 KV using a scanning electron microscope.

In-vitro ph-responsive drug-release study

Accurately weigh nanosponge equivalent to a known amount of Metformin HCl. Place it in the dissolution apparatus containing 100 mL of the selected medium. Maintain the required temperature, normally 37 ± 0.5°C. Maintain appropriate stirring speed according to your validated dissolution method. Withdraw a fixed volume, for example 5 mL, at predetermined intervals. Immediately replace the withdrawn volume with an equal volume of fresh medium maintained at the same temperature. Filter the withdrawn sample. Measure absorbance using a UV-visible spectrophotometer at the established λmax of Metformin HCl. Convert absorbance to concentration using your calibration equation. Calculate the amount released and % cumulative drug release. Repeat the experiment separately for pH 1.2, 4.5, 6.8 and 7.4.

Stability studies

Accelerated stability studies: -40 °C±2 °C/75%RH±5%RH. As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C/75%RH±5 % RH for a period of 6 mo. As per the standard protocol,

the samples must be analysed at 0, 1, 2, 3-and 6-months' time points. Accelerated stability studies were performed for the final optimized formulation. Samples were analysed at 1,2month' time points.

RESULT

Calibration curve of Metformin HCL

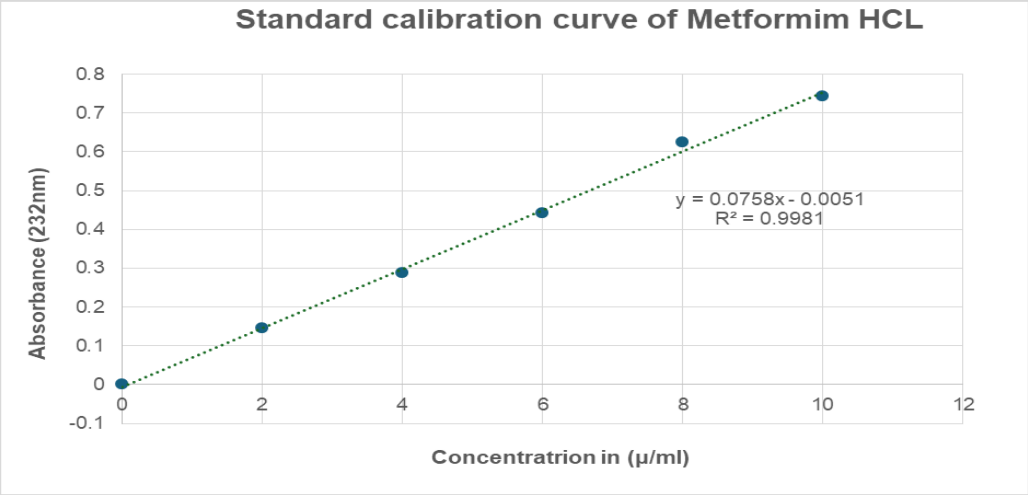

Fig-1.

Production yield

The production yield (PY) can be determined by calculating the initial weight of raw materials and final weight of nanosponges.

The percentage yield of different batches was determined by weighing the nanosponges after drying. The percentage yields of different formulations were found to be in the range of 79.81%-84.25%.

Table 2: Percentage yield of different batches of nanosponges.

S. No.	Batch	Yield (%)
1	F1	83.33
2	F2	84
3	F3	84.25
4	F4	80.44
5	F5	81
6	F6	79.81

Drug entrapment efficiency

The drug entrapment efficiency found in the range of 78.15% to92.89%. The increases concentration of polymer the drug entrapment efficiency also increases.

Table 3: Drug entrapment efficiency of different batches of nanosponges.

S. No.	Batch	Entrapment efficiency (%)
1	F1	78.15
2	F2	81.96
3	F3	85.82
4	F4	87.08
5	F5	92.5
6	F6	92.89

Determination of drug content

The various batches of the nanosponges were subjected for drug content analysis. The powdered nanosponges (30 mg) were dissolved in adequate quantity (100 ml) of phosphate buffer PH 6.8 then filter. The UV absorbance of the filtrate was measured using a UV spectrophotometer at 232 nm.

The drug content of different formulation was found to be in the range of 78.21% to 91.62% as shown in below table 4.

Table 4: Drug content values of different batches of nanosponges.

S. No.	Batch	Drug content (%)
1	F1	78.21
2	F2	84.36
3	F3	91.62
4	F4	88.32
5	F5	85.92
6	F6	83.76

Particle size analysis

The average particle size was obtained in range of 303 nm to 680 nm. The change in the concentration of polymer results in variation of particle size of nanosponges. The average particle size of formulation batch F3 showed Optimizedparticle size i.e. 418 nm while formulation batch F6 showed maximum particle size i.e. 680 nm. An increase in the concentration of polymer leads to increase in the particle size of nanosponges.

Table 5: Particle size of different batches of nanosponge.

S. No.	Formulation	Particle size
1	F1	303
2	F2	380
3	F3	405
4	F4	418
5	F5	519
6	F6	680

***In vitro* drug release study**

In vitro drug release for Metformin Hcl loaded nanosponges for a period of 24 h, was carried out by using Phosphate buffer (pH 6.8) at 37±50◦ C using cellophane membrane of 0.22 nm. From the dissolution profile of formulations F1 to F6, it is concluded that formulation batch F3 shows a better drug release profile than other formulations. Cumulative % release has been shown for average of three preparations, Cumulative % drug release for all the formulations are depicted in the table 6.

Table 6: *In vitro* drug release studies.

Time in (h)	% Drug release of nanosponges					
	F1	F2	F3	F4	F5	F6
1	4.9	6.0	8.8	12.6	5.5	3.9
2	7.8	12.4	15.8	20.3	8.2	5.9
3	10.4	18.8	22.5	28.6	12.1	8.3
4	14.2	25.9	30.0	36.9	16.7	12.4
5	18.4	32.7	38.8	43.3	20.9	16.8
6	23.8	39.9	46.7	50.2	24.9	20.2
7	28.0	46.5	54.5	56.2	28.6	25.5
8	34.1	53.7	62.2	62.1	32.5	30.1

9	40.1	60.3	69.3	68.5	36.6	35.7
10	46.2	66.9	75.6	73.7	40.6	40.7
15	58.6	76.6	84.9.	82.9	50.5	50.8
20	68.3	84.2	91.4	88.3	60.7	59.4
24	76.8	89.5	95.2	92.4	68.9	67.5

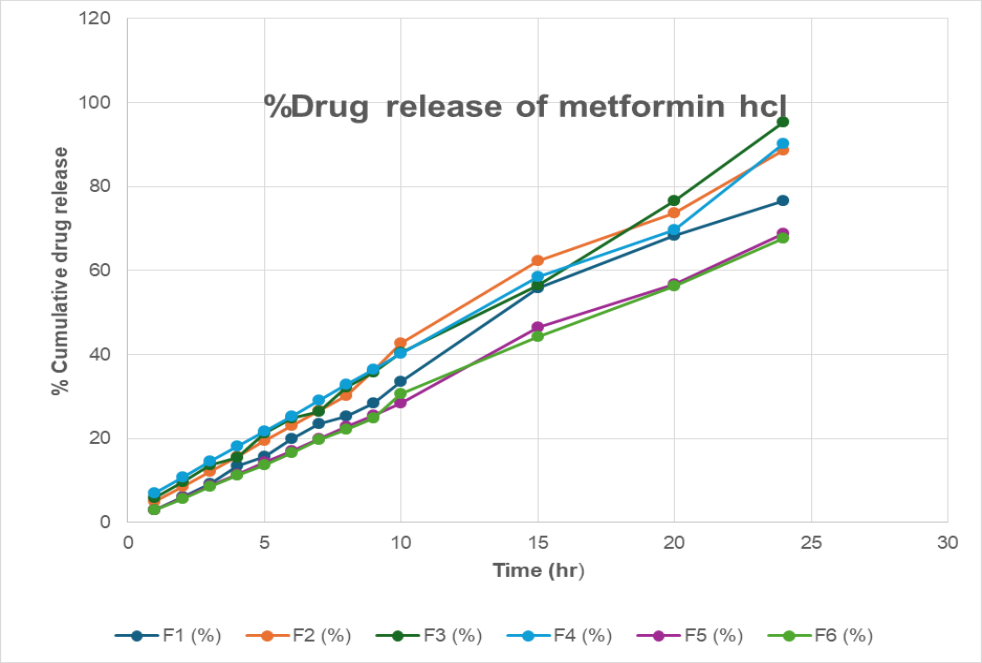

Fig. 2: Graphical presentation of % drug release of F1 to F6 batches.

Modeling of dissolution profile

In the present study, different release kinetic equations (zero order, first order, Higuchi equation and Korsmeyer-Peppas equation) were applied to interpret the release rate of drug from nanosponges. The data of *in vitro* release were fitted to these models and equations to explain the release kinetics of Metformin Hcl from nanosponges.

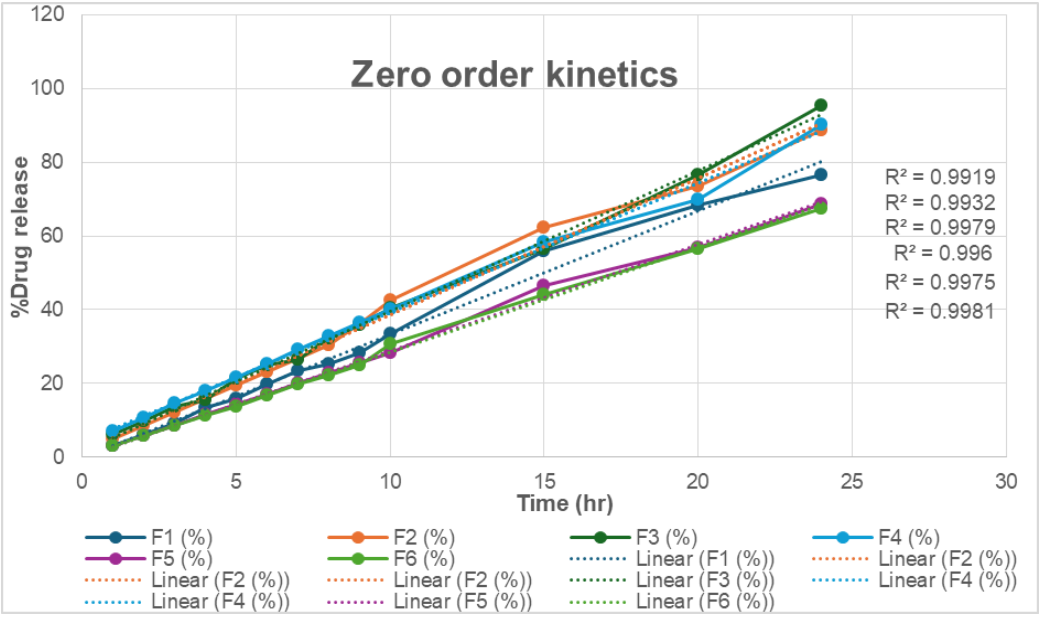

Fig. 3: Zero order release kinetics.

Fig. 4: First order release kinetics.

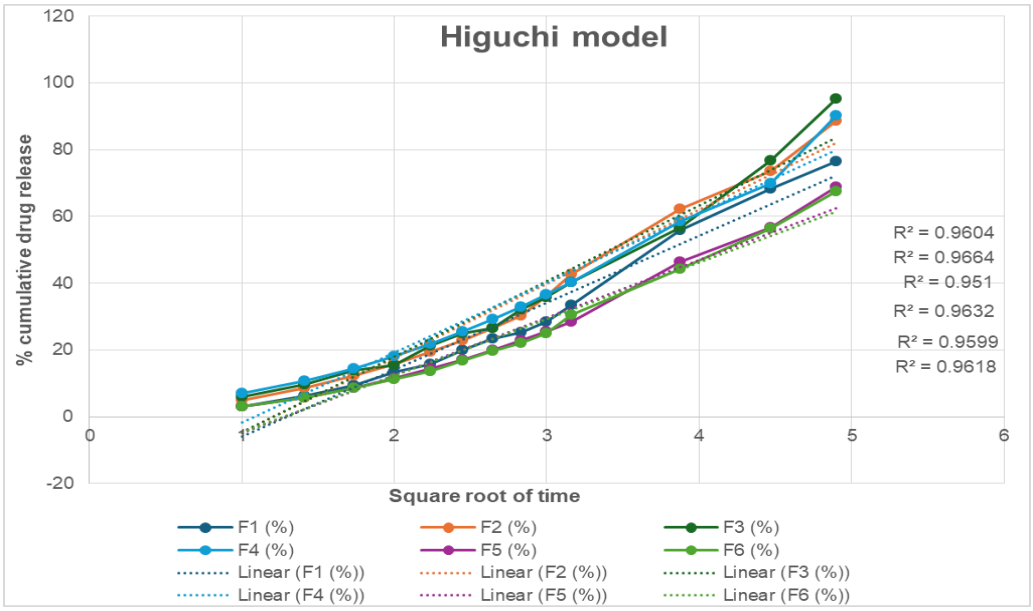

Fig. 5: Higuchi model.

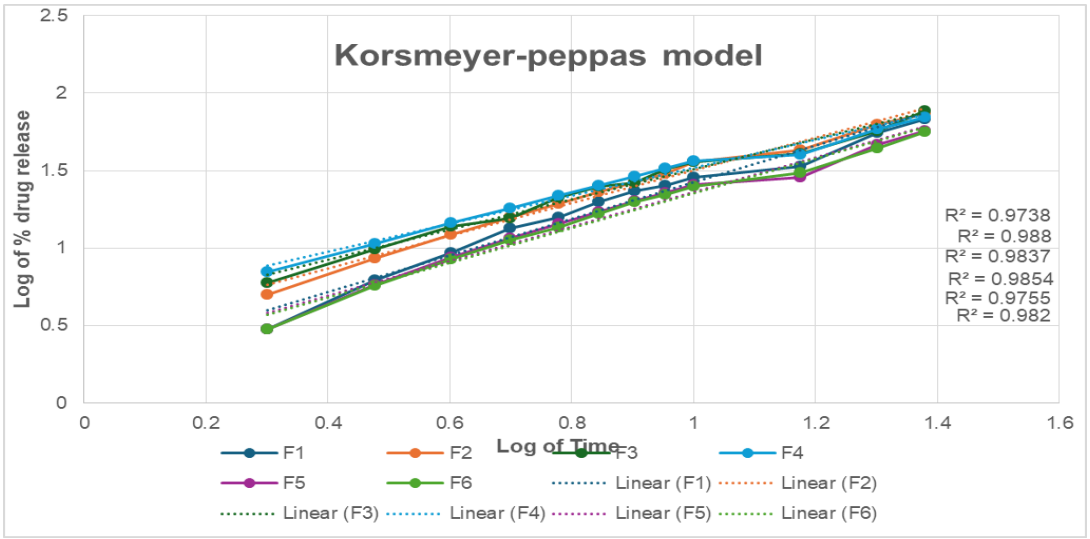

Fig. 6: Korsmeyer-Peppas model

Table 7: R^2values of different release kinetic models.

Formulation	Zero order kinetics R^2	First order kinetics R^2	Higuchi model R^2	Korsmeyer-Peppas model R^2
F1	0.9627	0.9932	0.0978	0.9821
F2	0.8806	0.9904	0.965	0.9613
F3	0.8463	0.9927	0.9464	0.9575
F4	0.8437	0.9882	0.9514	0.9638
F5	0.9679	0.997	0.9925	0.9891
F6	0.9592	0.9915	0.9796	0.9782

The *in vitro* release profile of the formulations indicates that the rate of drug release was higher for formulations, among all the formulations F3 shows more amount of drug release with the medium amount of polymer ratio. The plot of time vs cumulative % drug release in the zero-order kinetic model the regression coefficient value shows linearity as shown in (fig 3). The slopes and regression coefficient values (R^2) of various mathematical models for optimized batch F3, 0.9979,0.8445,0.951,0.9837 for zero order, first order, Higuchi and Peppas model respectively. The good linearity observed with the zero-order and regression coefficient value is higher. Hence this formulation is best fitted into zero-order release model.

CHEMICAL COMPATIBILITY STUDY

FT-IR Spectroscopy Studies

FT-IR spectroscopy gives information about possible interactions between the drug and the polymers. The FT-IR spectra of the pure drug, the individual polymers, and their physical mixture were recorded on a Shimadzu FT-IR spectrophotometer over the range 4000–400 cm^{-1}.

IR Spectrum of Metformin Hydrochloride

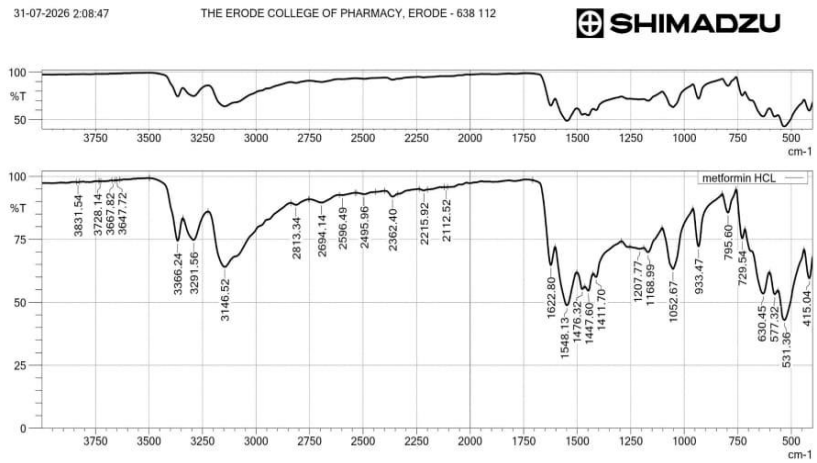

Fig. 7: IR Spectrum of Metformin Hydrochloride.

Table 8: FT-IR spectral interpretation of Metformin HCl.

Transition	Standard IR Range (cm^{-1})	Observed Value (cm^{-1})
N–H stretching	3500–3200	3366.24, 3291.56, 3176.52
C=N stretching	1650–1600	1722.80
N–H bending	1650–1500	1648.13
C–N stretching	1400–1200	1496.32, 1421.70, 1207.80
C–N stretching	1200–1000	1248.99, 1062.71
Fingerprint region	1000–650	932.47, 785.60, 739.54

IR Spectrum of Polyvinyl Alcohol

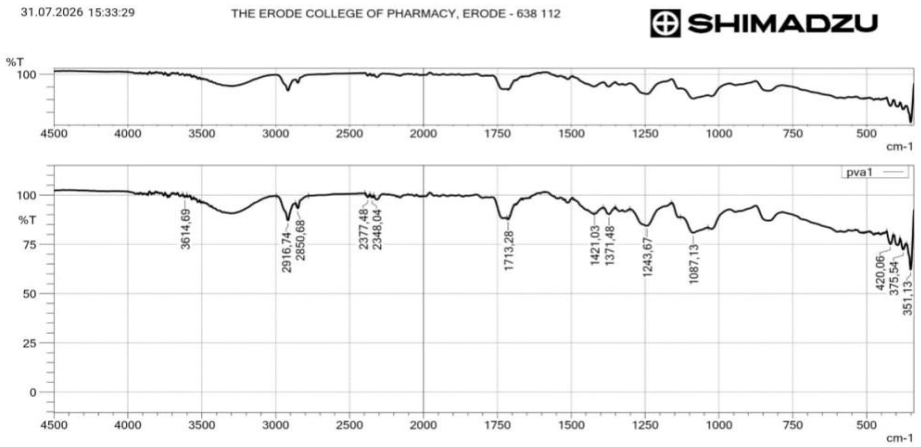

Fig. 8: IR Spectrum of Polyvinyl Alcohol.

Table 9: FT-IR spectral interpretation of polyvinyl alcohol.

Transition	Standard IR Range (cm^{-1})	Observed Value (cm^{-1})
O–H stretching	3600-3200	3594.69
C–H stretching	3000-2800	2826.74, 2950.78
C=O stretching	1750-1650	1715.38
C–H bending	1500-1400	1561.03
C–H bending	1400-1300	1451.48
C–O stretching	1300-1000	1343.67, 1977.13
Fingerprint region	1000-400	420.06, 375.54, 351.13

IR Spectrum of Ethyl cellulose

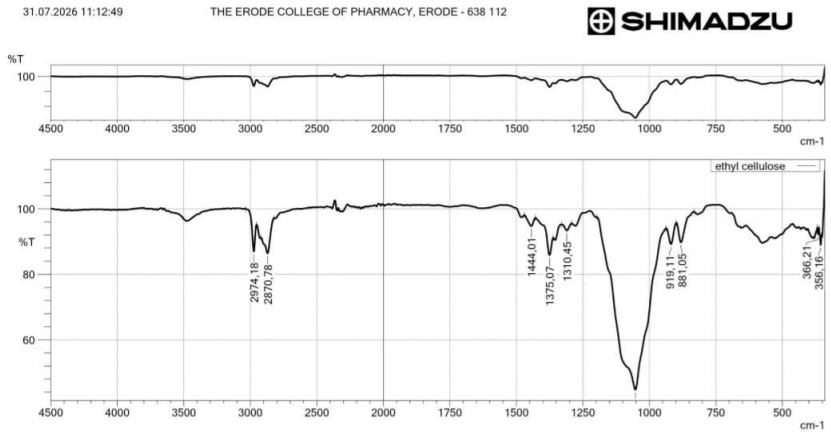

Fig. 9: IR Spectrum of Ethyl cellulose.

Table 10: FT-IR spectral interpretation of Ethyl cellulose.

Transition	Standard IR Range (cm^{-1})	Observed Value (cm^{-1})
C–H stretching	3000-2840	2974.18, 2870.78
C–H bending	1500-1350	1444.01, 1375.07
C–O–C stretching (ether)	1300-1000	1305.45
C–O–C / glycosidic linkage vibration	1000-800	919.91, 881.05
Fingerprint region	800-400	366.21, 356.16

IR Spectrum of Polyacrylic acid

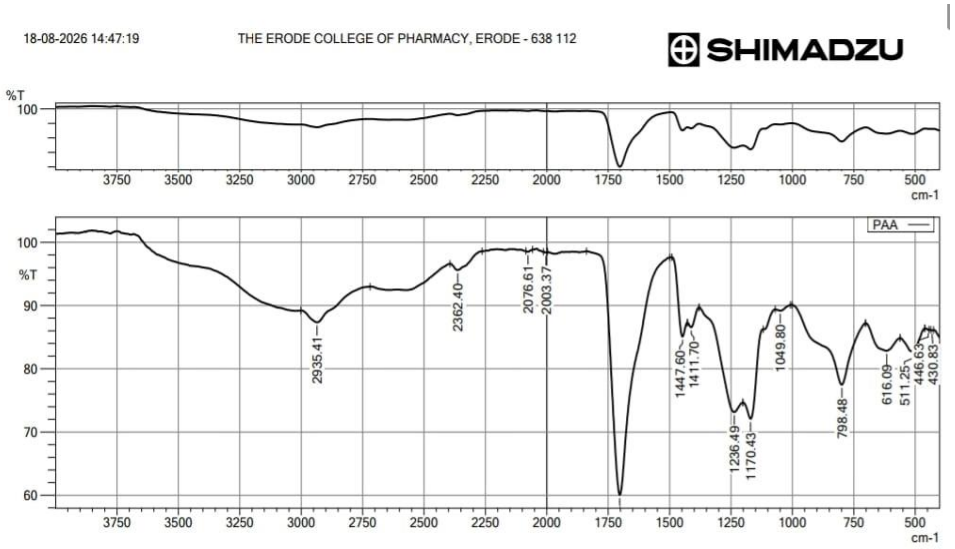

Fig. 10: IR Spectrum of Polyacrylic acid.

Table 11: FT-IR spectral interpretation of PAA.

Transition	Standard IR Range (cm^{-1})	Observed Value (cm^{-1})
O–H stretching	3500–2500	2935.41
C–H stretching	3000–2800	2935.41
C=O stretching (carboxylic acid)	1750–1650	1703.23
C–H bending	1500–1350	1447.60, 1411.70
C–O stretching	1300–1000	1236.49, 1170.43, 1049.80
C–C / skeletal vibration	1000–600	798.48, 616.09
Fingerprint region	600–400	511.25, 446.63, 430.83

IR Spectrum of nanosponge

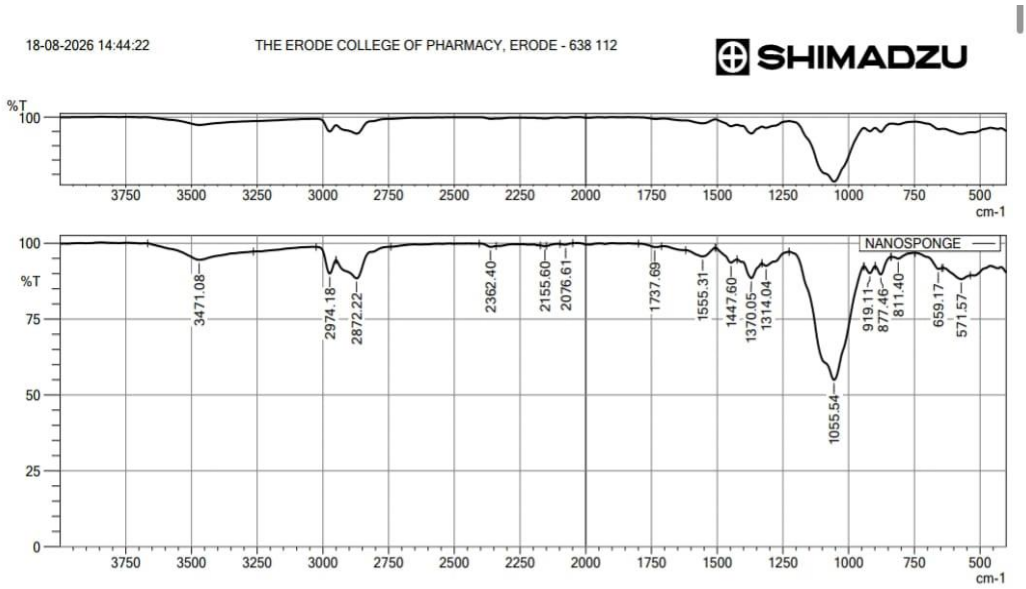

Fig. 11: IR Spectrum of nanosponge.

Table 12: FT-IR spectral interpretation of nanospnge.

Transition	Standard IR Range (cm^{-1})	Observed Value (cm^{-1})
O–H stretching	3550–3200	3471.08
C–H stretching	3000–2840	2974.18, 2872.22
C=O stretching	1750–1650	1737.69
N–H bending / deformation	1650–1500	1555.31
C–H bending	1500–1350	1447.60, 1370.05
C–O–C stretching (ether)	1300–1000	1314.04, 1055.54
C–O–C / glycosidic linkage vibration	1000–800	919.11, 877.46, 811.40
Fingerprint region	800–400	659.17, 571.57

INTERPRETATION

The FTIR spectrum of the optimized nanosponge formulation exhibits the characteristic absorption bands corresponding to the drug and polymers. The broad band at 3475 cm^{-1} represents O–H/N–H stretching vibrations, indicating that the hydroxyl and amine groups remain unaffected after formulation. The absorption bands at 2974 and 2872 cm^{-1} correspond to aliphatic C–H stretching vibrations. The strong peak at 1734 cm^{-1} is attributed to carbonyl (C=O) stretching of the polymer matrix. Peaks observed at 1449 and 1373 cm^{-1} are due to CH_2 and CH_3 bending vibrations, while the bands at 1311, 1278 and 1056 cm^{-1} correspond to C–O–C and C–O stretching vibrations characteristic of polymeric excipients. The fingerprint region below 1000 cm^{-1} remains unchanged, confirming preservation of the molecular structure.

The FT-IR spectra of Metformin HCl, PVA, Ethyl Cellulose, PAA and the prepared nanosponge showed the characteristic functional-group bands of the respective components. In the nanosponge spectrum, the major characteristic absorption bands were retained, with only minor shifts in some peak positions. No major disappearance of the characteristic functional-group bands was observed. Therefore, the FT-IR findings indicate that there was no major chemical interaction between Metformin HCl and the selected excipients, suggesting good drug–excipient compatibility and suitability of the excipients for nanosponge formulation.

SEM Studies

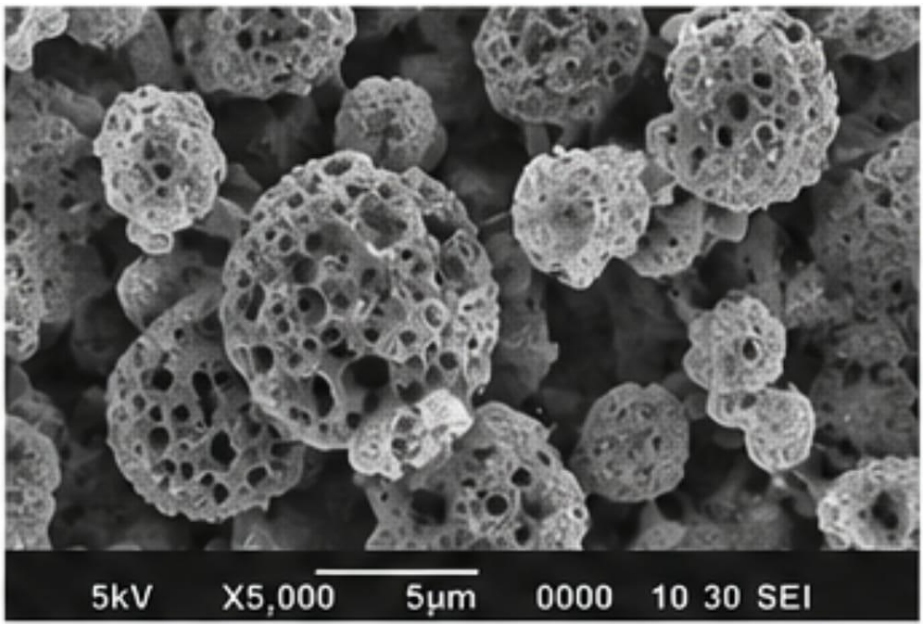

Fig. 12: Surface morphology.

In-vitro ph-responsive drug-release study

Table13: drug release of different pH

Time (h)	pH 1.2 (%)	pH 4.4 (%)	pH 6.8 (%)
1	4.61	6.58	9.22
2	6.58	9.22	13.18
3	7.91	11.20	16.47
4	9.88	13.84	19.75
5	11.20	15.82	23.08
10	15.82	19.54	36.30
15	20.44	22.68	50.96
20	24.40	26.29	65.38
24	28.30	32.96	76.24

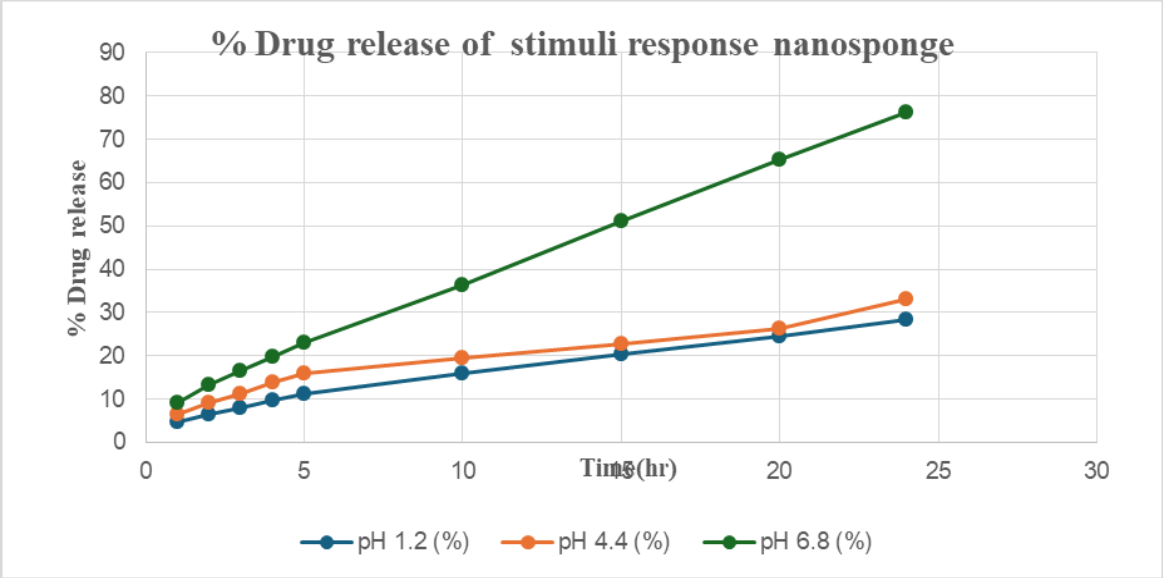

Fig. 13

The in-vitro drug-release study demonstrated a clear pH-dependent release behavior of the prepared stimuli-responsive nanosponge. Drug release increased progressively with increasing time at all tested pH conditions. The formulation showed relatively low drug release under acidic conditions. At pH 1.2, the cumulative drug release increased from 4.61% at 1 h to 28.30% at 24 h. At pH 4.4, drug release increased from 6.58% to 32.96% during the same period. A considerably higher release was observed at pH 6.8, where cumulative drug release increased from 9.22% at 1 h to 76.24% at 24 h. Thus, the formulation exhibited substantially greater drug release under the intestinal pH condition compared with the acidic conditions.

Stability studies

Optimized formulation was subjected to stability studies as per ICH guidelines. Various parameters such as drug content, and *in vitro* drug release were measured before and after 30, 60, days of stability. Results of stability studies are shown in below table 8. Results of stability studies showed there is no significant change in the abovementioned parameter after elevated temperature and humidity conditions during stability studies. Thus, it can be proved from the stability studies that the prepared formulation is stable and not much affected by elevated humidity and temperature conditions Stability studies.

Table 14: Stability study of optimized formulation.

Time (day)	Drug content (%)	*In vitro* drug release (%)
0	98.86	99.85%
30	98.20	99.74%
60	98.30	99.51%

DISCUSSION

The calibration curve of Metformin Hcl by UV method showed the linearity in absorbance and coefficient of regression found to be 0.9981. The IR studies shows that there is no interaction found between drug and excipients. All the characteristic peaks of Metformin Hcl were present in the spectrum of drug and prepared Metformin Hcl nanosponges, indicating compatibility in drug and polymer the spectrum confirmed that there is no significant change in the chemical integrity of the drug. The DSC thermogram pure Metformin Hcl shows sharp endothermic peak at 174˚C, which is its melting point as it melts with decomposition. Such a sharp endothermic peak indicates that Metformin Hcl used was in the pure crystalline state.

The percentage yield of different batches was determined by weighing the nanosponges after drying. The percentage yields of different formulations were found to be in the range of 83.33%-79.81%. The drug entrapment efficiency found in the range of 78.15 to 92.89. The increases concentration of polymer the drug entrapment efficiency also increases. The drug content of different formulation was found to be in range of 78.21 to 83.76. The average Particle size was obtained in range of 303 nm to 680 nm. The Change in the concentration of polymer results variation in particle size of nanosponges. An increase in the concentration of polymer leads to increase in the particle size of nanosponges. The SEM of the prepared nanosponges revealed a porous nature of Metformin Hcl nanosponges. Drug release data for the nanosponge formulation fitted into various release kinetic equations to find out order of drug release. The various release kinetic curves. The correlation coefficient showed that the release profile followed the zero-order drug release (R^2=0.9979) from these results it is apparent that the regression coefficient value closer to unity in case of zero-order kinetic model. The data indicate more linearity when plotted by the zero-order kinetic model. Hence, it can be concluded that the major mechanism of drug release follows zero-order kinetics.

The formulation showed relatively low drug release under acidic conditions. At pH 1.2, the cumulative drug release increased from 4.61% at 1 h to 28.30% at 24 h. At pH 4.4, drug release increased from 6.58% to 32.96% during the same period. A considerably higher release was observed at pH 6.8, where cumulative drug release increased from 9.22% at 1 h to 76.24% at 24 h. Thus, the formulation exhibited substantially greater drug release under the intestinal pH condition compared with the acidic conditions.

CONCLUSION

Nanosponge is the best novel drug delivery system. For improving the dissolution and bioavailability profile of poorly water-soluble drug. BCS class-3 drug are more suitable drug candidate for formulated into nanosponge. Nanosponges are able to encapsulate variety of various types of drug molecules. Nanosponges prepared by using emulsion solvent diffusion method are simpler and production cost of method is less. Nanosponge prepared by emulsion solvent diffusion method shows good entrapment efficiency ranged between 78.15to 92.89 and optimum drug release is 95.2%. The compatibility of drug and polymer determine by FT-IR, and DSC study. The result of IR and DSC shows drug and polymer are compatible to each other. The nanosponge formulation shows zero-order drug release. The outcome of the study concluded that Ethyl Cellulose are employed as polymer for oral drug delivery system. Nanosponges of

Metformin Hcl increases solubility and dissolution rate of drug. The emulsion solvent diffusion method is best method for preparation of nanosponges.

At pH 1.2, the cumulative drug release increased from 4.61% at 1 h to 28.30% at 24 h. At pH 4.4, drug release increased from 6.58% to 32.96% during the same period. A considerably higher release was observed at pH 6.8, where cumulative drug release increased from 9.22% at 1 h to 76.24% at 24 h. Thus, the formulation exhibited substantially greater drug release under the intestinal pH condition compared with the acidic conditions.

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