Original Article

Formulation and Evaluation of Nanosponges Loaded Hydrogel of Metformin Hydrochloride

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ABSTRACT

Objectives: The objective of the research is to formulate a nanosponges loaded hydrogel of Metformin Hydrochloride for the treatment of Psoriasis. Psoriasis is currently treated with a variety of topical and systemic therapies. Many of these treatments, however, are expensive and involve side effects, such as immunosuppression. As a result, there is a need to develop therapies that are effective, have fewer adverse effects, and are less expensive. **Materials and Methods:** The Solvent Emulsion Diffusion Process was used to create Metformin Hydrochloride nanosponges. Ethyl cellulose was used as a polymer, polyvinyl alcohol was used as an emulsifying agent, and an organic solvent mixture of Dichloromethane and Ethanol (1:1) was used to make nanosponges. The optimized batches of nanosponges were used for the formulation of Hydrogels using different gelling agents like Carbopol 934, HPMC K4, Sodium alginate and Acacia with same concentration. **Results:** The formulated Metformin Hydrochloride nanosponges were characterized by various tests like the Production yield, Entrapment efficiency, FT-IR, Zeta potential, Scanning Electron Microscopy, etc. Batch F5 showed the highest entrapment efficiency with the lowest particle size and hence was considered as the optimized batch for the formulation of the Hydrogels. The FT-IR ensured the compatibility of the drug with the polymer, the Zeta potential was good enough to produce formulations with good stability. The SEM analysis of batch F5 demonstrates that the nanosponges are segregated, spherical in shape with smooth surface and are porous in nature with particle size less than 1μ. **Conclusion:** Nanosponges loaded Hydrogel of Metformin HCl for the treatment of Psoriasis was successfully formulated, optimized and evaluated.

Keywords: Nanosponges, Metformin Hydrochloride, Topical Drug Delivery, Hydrogel, Psoriasis.

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INTRODUCTION

Advances in pharmaceutical technology have led pharmaceutical scientists to seek alternative routes other than oral / parenteral administration to deliver drugs efficiently and effectively to their target sites. Transdermal treatments are self-contained, discrete dose forms that release drugs via the skin when applied to intact skin. Because of its simplicity and affordability, topical administration is the primary method for delivering medicinal substances locally. When the medicine is applied to the topical surface, it avoids typical hepatic first-pass metabolism, gastric pH, and plasma level changes that occur when the drug is taken orally.[1,2]

The skin is an important site of local and systemic drug delivery. It is easily accessible, but has the unique property of being relatively impermeable. This means that a wide variety of products can be applied to the skin and removed again if necessary.[2,3]

Nanotechnology has finally found out alternative ways of targeting drug at the right sight and at the right time with minimal side-effects. Nanosponges are one such

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alternative. Nanosponges are types of nanoparticles that encapsulate the drug within the core made up of polymer and they circulate throughout the body to reach the site of action, and releases the drug in a predictable manner.[4,5]

Anti-diabetic hypoglycemia drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists, di-peptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, and biguanides, have been shown to be useful in the treatment of psoriasis. In addition, none of the hypoglycemic drugs appear to suppress the immune system. Off-label use of hypoglycemic medications to manage severe psoriasis and enhance quality of life while avoiding the harmful effects of other systemic medicines may be warranted for patients in whom immunosuppression is contraindicated.[5] Hypoglycemic medications can aid with psoriasis treatment, especially if you have diabetes or if immunosuppression isn't an option. Non-immunosuppressive therapeutics that effectively treat both psoriasis and diabetes would be appealing additions to the treatment ladder of dermatologists and endocrinologists' alike.[6,7]

Therefore the aim of the research was to combine nanotechnology with transdermal delivery system in order to increase the systemic delivery of the drug Metformin Hydrochloride, which would effectively transfer the drug into the skin and help treat Psoriasis.

MATERIALS AND METHODS

Materials

Holden Pharmaceuticals, Sinnar, Malegaon, Nashik, provided a free sample of Metformin Hydrochloride. HPMC K4, HPMC K15, Ethyl Cellulose, Eudragit L100, Ethanol, DMSO, Carbopol 934, Methyl Paraben, Propyl Paraben and Polyvinyl Alcohol, were purchased from Modern science, Nashik. Acacia and Sodium Alginate were obtained as gift sample. Dichloromethane was purchased from Bangalore Fine Chem, Bangalore. All the reagents and solvents used for the study were of Pharmacopoeial and Analytical grade.

Equipment used: Single Pan Electronic Balance (Contech CA224, Japan), Centrifuge (Remi, R-24), Ultrasonicator (Selecdtc 5033, Japan), Melting Point Apparatus (Kumar VMP-D, India), UV-Visible Double Beam Spectroscopy (Shimadzu 2450 Japan), Brookfield Viscometer (Brookfield LDV II+Pro), Magnetic Stirrer (Remi equipments Pvt. Ltd), FT-IR Spectroscopy (Shimadzu, 8400S, Japan), Differential Scanning Colorimetry (Shimadzu, DSC-60), Scanning Electronic Microscopy (Carl Zeiss, Germany, Supra 5), Digital pH meter (TOSHCON Industries, pH meter CL 54+).

Preformulation Studies

The physicochemical properties of the drug play a very important role in performance of the drug and the development of dosage form. Hence, in order to develop a safe, stable and effective dosage form the Preformulation study of Metformin Hydrochloride was carried effectively.

Solubility

The solubility of Metformin Hydrochloride was tested in different solvents like Distilled water, Ethanol, Dichloromethane, Methanolat ambient temperature, dissolving a specific amount of medication (10mg) in 10ml of each solvent. The solubility was detected visually and also using UV-visible spectroscopy.[7,8]

Melting point

Melting point determination device was used to determine the drug's melting point. The temperature of the device was gradually increased, and the temperature over which the drug commenced to melt and the temperature at which the drug totally melted were recorded.

UV-visible spectroscopy

Determination of lambda max

The structural information on Metformin hydrochloride's chromophoric component was obtained using a UV-Vis spectrophotometric approach. The solution was then analyzed in the range 200-400nm using UV/Vis Spectrophotometer to measure the Absorption maxima. 10mg of Metformin HCl was dissolved in 10ml Phosphate buffer (pH 7.4) and diluted up to 100ml using phosphate buffer.

Preparation of Calibration curve

A series of dilutions with concentration 2, 4, 6, 8, 10 ppm were prepared from Metformin Hydrochloride 100 ppm stock solution in phosphate buffer (pH 7.4) and were scanned at the determined Absorption maximum. Absorbance vs. Concentration graph was plotted.

Fourier Transform Infra-Red (FT-IR) Spectroscopy

FT-IR Spectroscopy was used to qualitatively identify the compound, providing adequate data on the groups present within the compound. The IR investigation was conducted using a Perkin Elmer Fourier Transform Infrared Spectrophotometer.

Preparation of Metformin Hydrochloride loaded Nanosponges

The Metformin Hydrochloride loaded Nanosponges were formulated by Emulsion Solvent Diffusion

Method. The polymer was chosen based on the results of experimental batches employing several polymers such as Ethyl Cellulose, HPMC K4, HPMC K15, and Eudragit L100 with the drug in 1:2 ratio. The results indicated that Ethyl Cellulose and Eudragit L100 were suitable for the formulation of Metformin Hydrochloride loaded Nanosponges. Hence, batches were prepared using Ethyl Cellulose as polymer with drug Metformin HCl in drug: polymer ratio varying from 1:1 to 1:6.

The internal phase (dispersed phase) is made up of a specific amount of medication and polymer that was dissolved in 20ml of organic solvent, 1% Dichloromethane and Ethanol, in a 1:1 ratio. The external phase (aqueous phase) is made up of a predetermined amount of polyvinyl alcohol dissolved in 100mL distilled water. Dropwise addition of the dispersed phase into the aqueous phase was done with a magnetic stirrer at 1000 rpm and then homogenized for 2 hr. Filtration was used to collect the nanosponges, which were then dried in a 40°C oven for 24 hr. After that, they were placed in a vacuum desiccator to remove any remaining solvent. The composition for formulation of nanosponges is given in Table 1.

Characterization of Metformin Hydrochloride Nanosponges

Production yield

The production yield was calculated accordingly –

$$\text{Production yield} = \frac{\text{Practical weight of Nanosponges}}{\text{Theoretical weight (Drug+Polymer)}} \times 100$$

Drug Entrapment Efficiency

Table 1: Composition of Metformin HCl loaded Nanosponges.

Formulation code	Dispersed phase			Aqueous phase	
	Drug (mg)	Polymer (mg) Ethyl Cellulose	1%DCM: Ethanol(ml) (1:1)	PVA (mg)	Distilled water (ml)
F1	50	50	20	500	100
F2	50	100	20	500	100
F3	50	150	20	500	100
F4	50	200	20	500	100
F5	50	250	20	500	100
F6	50	300	20	500	100

A mortar pestle was used to crush an appropriate amount of Metformin HCl loaded nanosponges. Phosphate buffer (pH 7.4) was used to suspend 10 mg of nanosponges in 10 ml. After 24 hr, the solution was filtered, and the filtrate was diluted with phosphate buffer before being examined using a UV Vis Spectrophotometer.[8] The following formula was used to estimate the Drug Entrapment Efficiency-

$$\text{Drug Entrapment Efficiency} = \frac{\text{Experimental drug loading}}{\text{Theoretical drug loading}} \times 100$$

Infrared Spectroscopy

Metformin HCl loaded nanosponges formulation's FTIR spectra was recorded. A few milligram of Metformin HCl nanosponges (F5) were weighed and combined with 100 milligram of potassium bromide (dried at 40°-50°C). The combination was then compacted into a pellet using a hydraulic press with a 10-ton pressure. The pellet was then scanned with an IR Spectrophotometer in the wavelength region of 4000-400 cm^{-1}.[9,10]

Particle Size

The average mean width and particle sizes of loaded nanosponges were investigated employing the Brookhaven instrument and the Dynamic Light Scattering method. To obtain the correct light scattering intensity for Metformin HCl nanosponges, the dried nanosponges were distributed in distilled water.[10]

Zeta Potential

The nature and composition of the environment, as well as the surface charge of the particle, anything adsorbed to the interface and nature and composition of the surrounding, all influence the zeta potential. A zeta sizer containing zeta cells and gold plated polycarbonate cells can be used to calculate the surface charge of the nanosponges. The zeta potential is crucial in determining the stability of nanosponges.[10,11]

Scanning Electron Microscopy

The surface morphology of the synthesized Metformin HCl nanosponges was evaluated using scanning electron microscopy (SEM).[10,11]

Preparation of Metformin Hydrochloride Nanosponges Hydrogel

1gm of gelling agent was dispersed in 5ml Distilled water and allowed for swelling overnight. Gelling agents used for the formulation of nanosponges were Carbopol 934, Sodium Alginate, HPMC K4 and Acacia. The weighed quantities of other excipients were

Table 2: Composition of Metformin HCl nanosponges Hydrogel containing different polymers.

Ingredients	F1	F2	F3	F4
Drug loaded Nanosponges (mg)	50	50	50	50
Carbopol 934 (gm.)	1	-	-	-
HPMC K4 (gm.)	-	1	-	-
Sodium Alginate (gm.)	-	-	1	-
Acacia (gm.)	-	-	-	1
Methyl Paraben (gm.)	0.1	0.1	0.1	0.1
Propyl Paraben (gm.)	0.05	0.05	0.05	0.05
1% DMSO (ml)	10	10	10	10
Water (ml) q.s.	20	20	20	20

added to the previously soaked Gelling agents with continuous stirring for 1-2 hr. The pH of the gel was adjusted using Triethanolamine (TEA). TEA is used for all the polymers. After that, the gel was transferred to a measuring cylinder, and the volume was adjusted to 20ml by adding distilled water. The formula for preparation of the hydrogels is given in Table 2.

Characterization of Metformin Hydrochloride Nanosponges Hydrogel

Physical evaluation

The clarity and Homogeneity of the formulation was observed. pH of the formulated hydrogel was measured using the digital pH meter.

Viscosity

The viscosity of the prepared gel was measured and recorded using the Brookfield viscometer spindle LV6 at various rpms.

Spreadability

1gm of gel was used to check the spreadability of the formulated gel. The gel was placed between the 2 glass slides of the spreadability apparatus, weight was tied to the upper glass slide and the time required to slide over both slides from gel was noted.[12] The spreadability of the formulated gel was calculated using the following formula –

$$S = M*L/T$$

Where, **S** = Spreadability, **M** = weight tied to the upper slide, **L** = length of the glass slide (L = 7.5cm), **T** = time taken to separate the 2 slides (sec.).

Actual Drug content

In order to determine the actual drug content 1gm of gel was suspended in 100ml of Phosphate buffer (pH 7.4). 1ml of the solution was then diluted upto 10ml. The concentration of Metformin HCl in the formulated gel was determined by measuring the absorbance of all four samples at 232.6nm using UV-visible spectroscopy.[13]

RESULTS AND DISCUSSION

Evaluation of Metformin Hydrochloride loaded Nanosponges

Physical Characteristics

Metformin Hydrochloride was checked for its colour, odour and texture. The Metformin HCl powder was found to be white, odorless, crystalline and hygroscopic in nature. The melting point was observed to be in the range 223°C - 226°C, the outcome is identical to that stated in the reference. In distilled water, the medication was found to be readily soluble, somewhat soluble in ethanol and methanol, and insolvable in DCM. Hence, a mixture of ethanol and dichloromethane was used in equal proportion (1:1) as the organic solvent for the preparation of internal phase in the formulation of nanosponges as it gave better results than ethanol alone.

Determination of Absorption Maxima

In phosphate buffer (pH 7.4), the absorption maximum of Metformin Hydrochloride was determined to be 232.6nm which is very close to the pharmacopoeial standard i.e. 233nm (Figure 1). The absorbance for the dilutions of Metformin Hydrochloride for 2,4,6,8 and 10ppm were recorded at the λ_{max}. Absorbance vs.

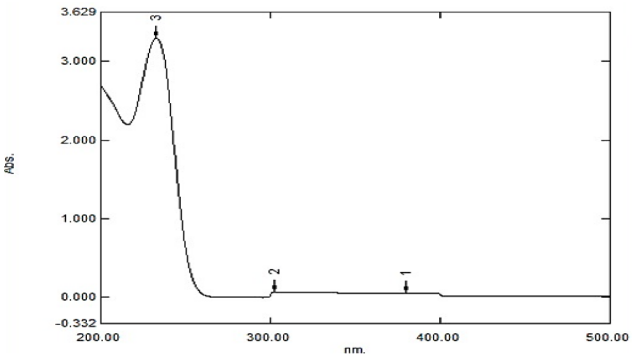

Figure 1: Metformin Hydrochloride UV Absorption Spectrum in Phosphate Buffer (pH 7.4).

The λ_{max} was found to be 232.6nmConcentration(µg/ml)	Absorbance
0	0
2	0.084
4	0.233
6	0.353
8	0.498
10	0.613

Concentration graph was plotted and linearity was obtained with an $R^2 = 0.9961$ as shown in the Figure 2.

The Solvent Emulsion Diffusion method was found to be simple and suitable for the laboratory scale preparation of Metformin Hydrochloride nanosponges. Based on the entrapment efficiency of the drug Ethyl cellulose was selected as the polymer for the formulation of the nanosponges.

Production yield percent is represented in the Table 3. The production yield for all the formulated batches was observed in the range 27% to 78.33%. The F4 batch gave the highest production yield (78.33%) whereas F1 batch gave the lowest production yield (27%). It was observed that with the increase in the polymer concentration there was an increase in the production yield i.e. F6>F5>F4>F3>F2>F1.

Entrapment Efficiency for the Metformin Hydrochloride loaded nanosponge batches F1 to F6 was determined using UV visible spectroscopy. Batch F5 showed the highest entrapment efficiency of approximately 97.69% whereas batch F4 showed the lowest entrapment efficiency of approximately 86.73%. The entrapment efficiency of all the batches was found to be in an increasing order as F5>F2>F6>F3>F1>F4 is illustrated in the Table 3 and Figure 3.

Particle size analysis is one of the most important characteristic property of nanosponges and therefore was performed for all the 6 batches. All of the formulations' mean particle size was found to be in the nanoscale range, as shown in the Table 3 with batch F5 with the lowest mean particle size of approximately 196.39nm as illustrated in the Figure 4. The mean particle size of all the formulations was found to be in decreasing order as F4>F3>F1>F2>F6>F5. The particle size of nanosponges should be less than 1µ. All of the batches had a mean particle size of less than 1µ, ensuring thauT 1 1µ

with zeta potential greater than +25 mV or less than -25 mV typically have highest stability. The observations are illustrated in the Table 3. The best formulation selected was batch F5 on the basis of zeta potential analysis. For Metformin HCl nanosponges with ethyl cellulose (F5) the zeta potential was found to be -23.03mV with peak area of 100% intensity. These value indicate that the formulated F5 batch is stable. The zeta potential report of batch F5 is illustrated in Figure 5.

IR spectrum for the pure drug Metformin Hydrochloride, physical mixture of drug and polymer and for the optimized batch F5 was taken and all the characteristic peaks were observed as depicted in the Figure 6, 7 and 8 respectively. The peaks present in the FT-IR of pure Metformin HCl are present in the physical mixture containing the drug with polymer Ethyl cellulose. It is therefore evident that Metformin Hydrochloride is compatible with Ethyl cellulose and can therefore be chosen as the polymer for the formulation of nanosponges.

Surface Morphology

Particle size and morphology of nanosponges were also studied by scanning electron microscopy SEM). The SEM images of the optimized F5 batch showed the typical morphological aspects of nanosponges. Figure 9 confirmed that the nanosponges are segregated, spherical in shape with smooth surface and are porous in nature with particle size less than 1µ.

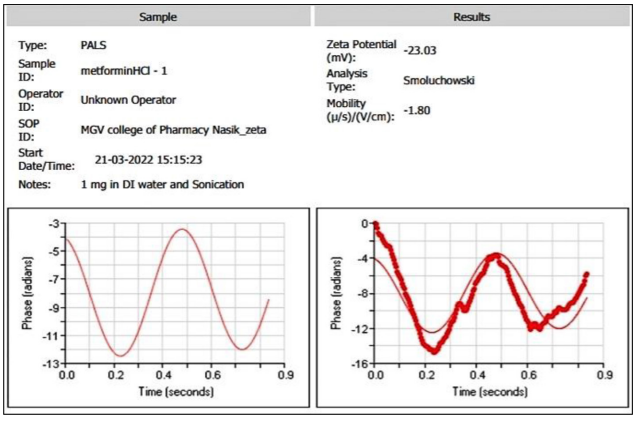

Figure 5: Zeta Potential report for batch 5 (F5).

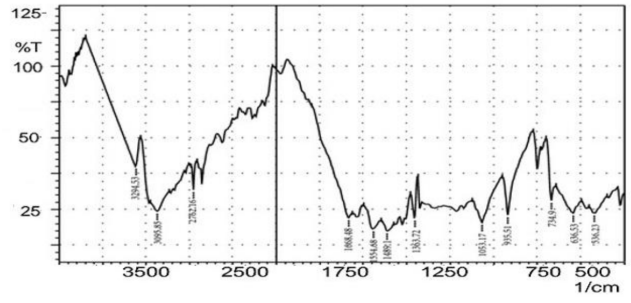

Figure 6: IR Spectrum of Metformin Hydrochloride (Drug).

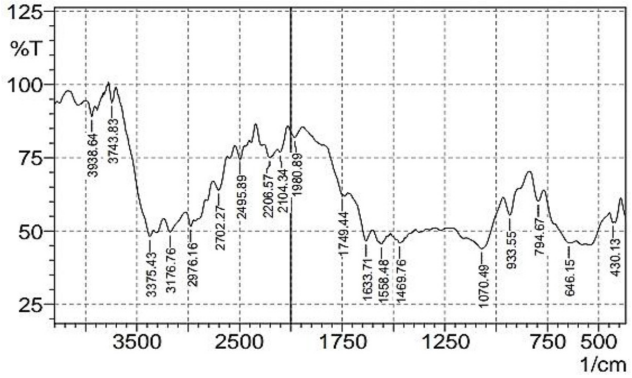

Figure 7: IR Spectrum of Metformin Hydrochloride and Ethyl cellulose (Drug + Polymer).

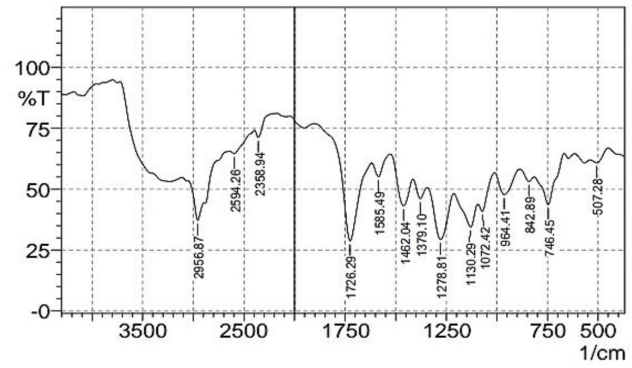

Figure 8: IR Spectrum of Metformin Hydrochloride loaded nanosponges (F5)

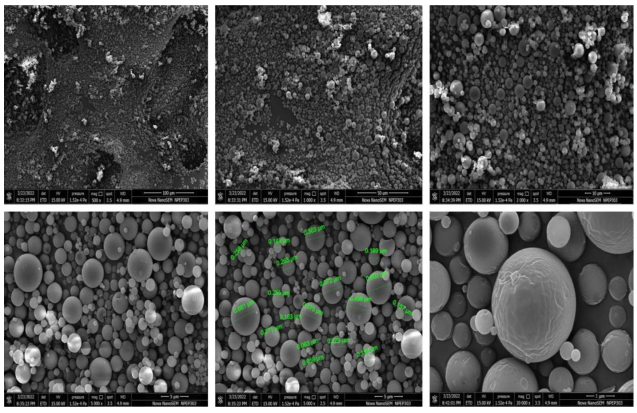

Figure 9: SEM Analysis report for batch 5 (F5).

Evaluation of Metformin Hydrochloride Nanosponges Hydrogel

Physical Characteristics

The physical characteristics of the formulated batches of Hydrogel (F1 to F4) i.e. clarity, homogeneity, pH, spreadability and viscosity was observed. The pH of

Table 4: pH, Spreadability, Homogeneity and Actual Drug Content % of formulations (F1 to F4).

Formulation batch	pH	Spreadability	Homogeneity	Actual Drug Content %
F1	5.57	41.67	Good	78.65
F2	5.63	62.5	Good	71.89
F3	5.25	53.57	Good	78.71
F4	5.38	83.33	Good	72.23

Table 5: Viscosity study of formulations (F1 to F4).

Formulation batch	RMP	Viscosity (cp)
F1	10 25 50 70 100	17037 9358 7678 5783 4451
F2	10 25 50 70 100	9856 7246 6538 4692 2355
F3	10 25 50 70 100	15637 8932 7653 5214 4039
F4	10 25 50 70 100	7358 5783 3467 3016 2124

the Hydrogels was determined using Digital pH meter. The pH of the hydrogels was found to be in the range of 5 to 6. The normal pH of the skin lies in the range 4.5 to 5.5. Extremes of pH on acidic or basic side can always cause irritation to the skin or redness. Hence, the pH determined for the Hydrogel formulations was found to be suitable for application on the skin. The results obtained for pH, Spreadability, Homogeneity and Actual Drug Content % of formulations is given in Table 4.

The viscosity of all the formulated batches of Hydrogel consisting of four different types of gelling agents – Carbopol 934, HPMC K4, Sodium Alginate and Acacia was measured using the Brookfield Viscometer at varying rpm. The viscosity of the batches was found to be in an increasing order as F1>F3>F2>F4. The viscosity of batch F1 consisting of Carbopol 934 was found to have the highest viscosity, whereas batch F4 consisting of Acacia was found to have the lowest viscosity. The viscosity of all the formulated Hydrogels is illustrated in the Table 5.

Table 6: % Drug release study of Hydrogel formulations (F1 to F4)

Time (Hrs.)	F1	F2	F3	F4
0	0	0	0	0
1	28.56	14.33	21.36	17.89
2	30.45	18.34	29.65	19.83
3	38.65	21.93	33.29	23.49
4	41.51	34.26	38.66	36.72
5	47.93	35.19	40.35	39.26
6	59.76	44.67	57.14	49.54
7	69.21	55.28	63.44	57.95
8	75.63	59.98	71.69	68.54

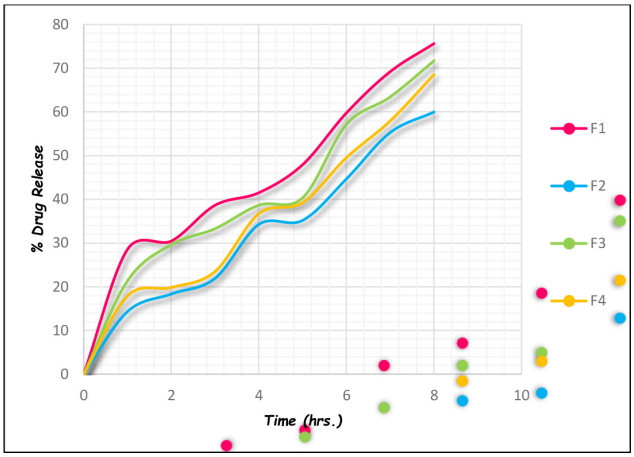

Figure 10: % Drug Release of Nanosponges loaded Hydrogels (F1 to F4)

The diffusion rate studies were performed to evaluate the diffusion characteristics of Metformin HCl from the prepared nanosponges Hydrogel. Table 6 and Figure 10 shows the release profile of all the batches. The percentage drug release for all the hydrogels was found to be in the range 59.98% to 75.63% within given time period. From the results obtained the hydrogel containing Carbopol 934 as the gelling agent (F1) shows the highest drug release in comparison to the other 3 batches. Whereas, hydrogel containing HPMC K4 as the gelling agent (F2) shows the lowest drug release as compared to other Hydrogels.

CONCLUSION

In the present study, Metformin HCl has been successfully incorporated in nanosponges. From the observations and the test results obtained it can be speculated that all the formulations showed satisfied

properties. The Metformin HCl loaded nanosponges were formulated by Solvent emulsion diffusion method and were then examined for various parameters like Physical properties, Production yield, Entrapment efficiency, Particle size, Zeta potential for nanosponges. The study confirmed that batch F5 showed the highest entrapment efficiency with the lowest particle size and hence was considered as the optimized batch. Hence F5 batch was further subjected for Surface morphology study. The entrapment efficiency and the average particle size for the optimized batch (F5) was found to be 97.69% and 219.76nm respectively. Metformin HCl loaded nanosponges gel was prepared and evaluated for viscosity, pH and *in-vivo* drug diffusion study. Metformin HCl can be formulated into low dose nanosponges loaded hydrogel for the treatment of psoriasis with concomitant diabetes. This study therefore recommended for further extensive research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SEM: Scanning Electron Microscopy; **FT- IR:** Fourier Transform Infrared Spectroscopy; **DMSO:** Dimethyl Sulfoxide; **HPMC:** Hydroxy Propyl Methyl Cellulose; **rpm:** Rotation per minute; **°C:** Degree Celsius.

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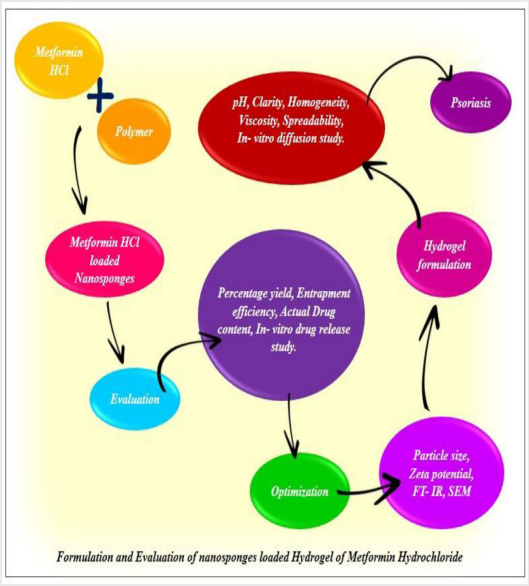
SUMMARY

Metformin Hydrochloride nanosponges were formulated by Solvent Emulsion Diffusion method using different polymers. The formulated nanosponges were then characterized for various evaluation parameters like FTIR, SEM, Zeta potential, *in- vitro* drug release. The FT-IR ensured the compatibility of the drug with the polymer, the Zeta potential was good enough to produce formulations with good stability. The SEM analysis of batch F5 demonstrated that the nanosponges are segregated, spherical in shape with smooth surface and were porous in nature with particle size less than 1μ. The study proved that Metformin HCl can be formulated into low dose nanosponges loaded hydrogel for the treatment of psoriasis with concomitant diabetes. This study is therefore recommended for further extensive research.

PICTORIAL ABSTRACT



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