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Formulation and evaluation of gel-loaded microsponges of diclofenac sodium for topical delivery

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Abstract
In this study ethyl cellulose facilitated microsponges were prepared by the double emulsification technique (Quasi emulsion technique) and subsequently dispersed in a carbopol gel base for controlled delivery of diclofenac sodium to the skin. The microsponges formulations were prepared by quasi-emulsion solvent diffusion method employing ethyl cellulose as a polymer. The compatibility of the drug with formulation components was established by Fourier Transform Infra-Red (FTIR) spectroscopy.
The surface morphology, particle size, production yield, and drug entrapment efficiency of microsponges were examined. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. Particle size of prepared microsponges was observed in the range of 28.7 ± 1.02-23.9 ± 1.19 µm. Scanning electron microscopy revealed the porous, spherical nature of the microsponges. SEM photographs revealed the spherical nature of the microsponges in all variations; however, at higher ratios, drug crystals were observed on the microsponge surface.
Increase in the drug/polymer ratio (1:1 to 1:10) increased their yield (10.85 ± 1.60 to 41.03 ± 1.26), average particle size of all formulations ranges from 28.7 µm to 45.9 µm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of drug to polymer was increased, the particle size decreased, The pH of the gel was determined having average pH of 7.3 ± 0.4, The viscosity of the formulation was analysed by Brookfield viscometer with maximum reading of 2874 and minimum reading of 2345 cps, the drug content of different formulations was found in the range 19.07 ± 2.21 to 33.09 ±2.27, the spredibility of gel containing microsponges revealed in the range of 13.6 ± 0.89 to 13.6 ±0.91 showing good characteristics of spreading, the cumulative release of the formulations are in the range of 89.83% to 13.25%.

Keywords: Ethyl Cellulose, Microsponge Delivery System (MDS). Scanning Electron Microscopy (SEM), UV Spectroscopy.

1. Introduction
Microsponges are tiny, sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. Microsponge delivery systems (MDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and in RNAi silencing [1].
The proposed work involves formulation and evaluation of Diclofenac sodium microsponge formulation by using Ethyl Cellulose as polymer by quasi emulsion process. And finally the optimized Diclofenac sodium microsponges formulate on are incorporated into gel to apply on the skin tissue as Transdermal drug delivery system. Hence, in the present work an attempt was to develop controlled release microsponges using synthetic polymer to minimize frequent dosing, prolong the pharmacological effect and thus improve patient compliance.

2. Materials and Methods
Diclofenac sodium is a gift sample from suncare formulation Pvt. Ltd, Dehradun. Ethyl Cellulose, PVA and Carbopol 940 were purchased from Central Drug House Ltd, New Delhi

2.1 Method of Preparation of Microsponge
Microsponges of Diclofenac Sodium and Ethyl Cellulose was prepared by quasi-emulsion solvent diffusion method according to the formula given in table no 1, the process involved formation of quasi-emulsion of two different phases i.e. internal phase and external phase similar to emulsions. Table no 1 gives the detailed information about the prepared formulations.

1. The internal phase of drug-polymer solution (1: different ratio) made in a volatile solvent dichloromethane (10 ml).
2. And then it was added to external phase comprising the aqueous 5% (5 mg/100 ml water) polyvinyl alcohol (PVA) solution with vigorous stirring.
3. Glycerol (1-2 ml), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called quasi-emulsion globules.
4. The stirring was continued upto 6 hrs till the insoluble, rigid microparticles i.e. microsponges is formed.
5. Then it was filtered to separate the microsponges
6. The microsponges were then dried in an air heated oven [2-4].

Table 1: Table revealing the master formula for microsponge formulation.

S. No.	Ingredient (mg/ml/gm)	M1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10
1	Diclofenac sodium	1	1	1	1	1	1	1	1	1	1
2	Ethyl cellulose	1	2	3	4	5	6	7	8	9	10
3	Polyvinyl alcohol	500	500	500	500	500	500	500	500	500	500
4	Dichloromethane	10	10	10	10	10	10	10	10	10	10
5	Glycerol	1	1	1	1	1	1	1	1	1	1
6	Water	100	100	100	100	100	100	100	100	100	100
7	Drug: Polymer	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9	1:10

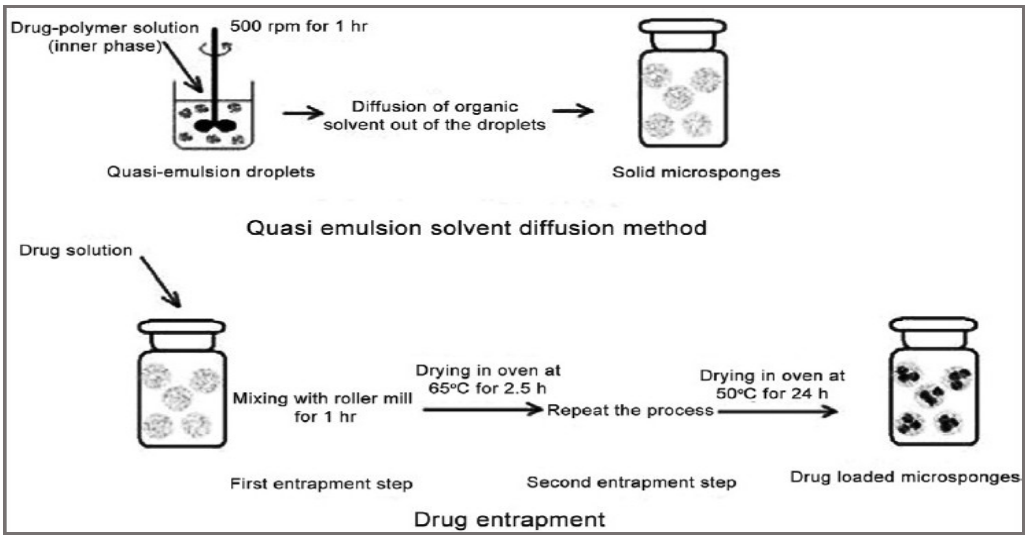

Fig 1: Image Showing Quasi-emulsion solvent diffusion method set up.

Once the formulation was prepared characterization were done by determining percent yield, drug content, particle size, Fourier Transform Infrared (FTIR), surface morphology by Scanning Electron Microscopy (SEM) and *In-vitro* study.

2.2 Preparation of Diclofenac Sodium Microsponge Gel

Gel of Diclofenac Sodium was prepared by using following formula given in table no. 2. A clear dispersion of Carbopol was prepared in water using moderate agitation.

Table 2: Table revealing the master formula for gel formulation

S No.	Ingredient	Quantity (mg/ml)
1	Carbopol 934 P	35
2	Triethanolamine	2
3	Methyl paraben	3
4	Propyl paraben	1
5	Distilled water	q.s

1. A clear dispersion of carbopol (35 mg) is prepared in water (q.s) using moderate agitation.
2. Triethanolamine (1-2 drops) is used to neutralise the formulation and subsequently preservatives Methyl paraben (3 mg) and Propyl paraben (1 mg) was added to resist the microbial growth.
3. And then volume was maintained with water. Gel prepared were degassed with ultrasonication.

3. Results [5-7]

A) Particle size analysis of Microsponges

The particle size of the microsponge was determined by optical microscopy and the microsponges were found to be uniform in size. The average particle size of all formulations ranges from 28.7 µm to 45.9 µm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer

ratio, the amount of polymer available per microsponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the drug and reducing the thickness of polymer wall and microsponges with smaller size were obtained.

By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio.

Table 3: Table revealing the results of Particle size analysis of Microsponges

S. No.	Formulation code	Particle size (µm) (mean ± S.D) n=3
1	M1	28.7 ± 1.02
2	M2	29.8 ± 1.00
3	M3	31.8 ± 1.05
4	M4	33.7 ± 1.54
5	M5	37.2 ± 1.32
6	M6	31.3 ± 1.25
7	M7	31.9 ± 1.17
8	M8	29.4 ± 1.23
9	M9	27.5 ± 1.26
10	M10	23.9 ± 1.19

B) Morphology determination by scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared microsponges. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10^{-10} to 10^{-12} grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens.

It was observed that the microsponges were spherical, and uniform with no drug crystals on the surface. The shape of the microsponges affects the surface area and surface area per unit weight of spherical microsponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.

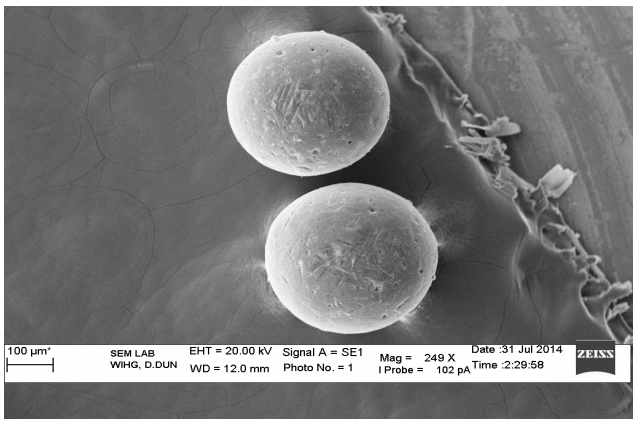

Fig 2: Image Showing Microsponge structure at 249x

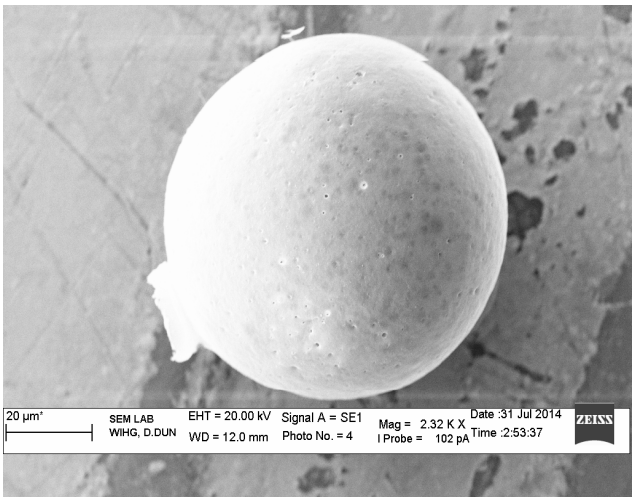

Fig 3: Image Showing Single spherical Microsponge at 232x

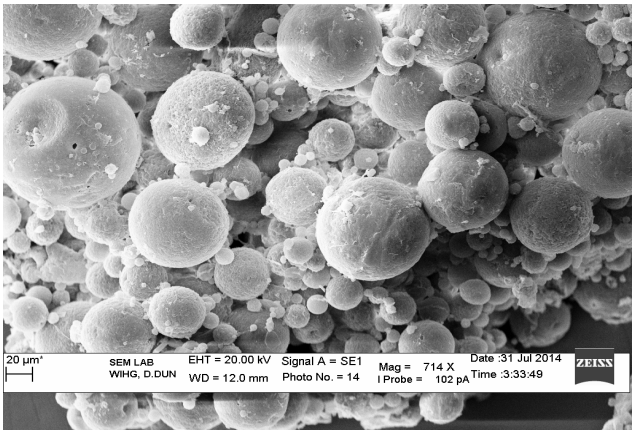

Fig 4: Image Showing clusters of Microsponge at 714x

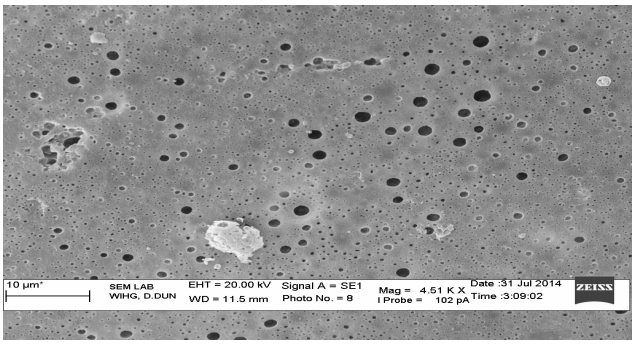

Fig 5: Image Showing Showing highly porosity of the Microsponges at 451 KX

C) Percentage yield

It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the Practical yield was calculated as Microsponges recovered from each preparation in relation to the sum of starting material (Theoretical yield). It can be calculated using following formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield (drug + polymer)}} \times 100$$

The loss of product was due to the formation of some agglomerates and polymer adherence to the container as a result of a viscous nature of slurry. It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production and in this experiment, it is revealed that with increase in polymer ratio the percent yield also increase.

Table 4: Table revealing the results of Percent yield

S. No.	Formulation code	Theorotical yield (mg)	Practical yield (mg)	Percent Yield (%) (mean ± S.D) n=3
1	M1	2000	217	10.85 ± 1.60
2	M2	3000	389	12.96 ± 1.80
3	M3	4000	523	13.07 ± 1.78
4	M4	5000	753	15.06 ± 1.67
5	M5	6000	1112	19.53 ± 1.54
6	M6	7000	1834	26.21 ± 1.02
7	M7	8000	1936	24.20 ± 1.77
8	M8	9000	2761	30.60 ± 1.65
9	M9	10000	3612	36.12 ± 1.56
10	M10	11000	4513	41.03 ± 1.26

D) Drug content

The drug content was determined by using phosphate buffer (pH 7.4) with the help of UV- spectrophotometer by dissolving the formulation in phosphate buffer for 24 hrs and then the sample was taken and analysed in UV- spectrophotometer.

With this evaluation parameter of Microsponge it was revealed that the formulation M4 have the Drug content greater i.e. 74.03 mg and after that the drug content is decreasing with increase in content of polymer due to improper carrying of drug by the polymer.

Table 5: Table revealing the results of Drug content studies

S. No.	Formulation code	Drug content (%) (mean ± S.D) n=3
1	M1	19.07 ± 2.21
2	M2	27.82 ± 2.12
3	M3	38.67 ± 2.13
4	M4	74.03 ± 2.25
5	M5	69.85 ± 2.31
6	M6	63.02 ± 2.16
7	M7	58.01 ± 2.21
8	M8	51.06 ± 2.34
9	M9	3705 ± 2.19
10	M10	33.09 ±2.27

E) Spredibility test

Spreadability of gel was determined manually in which an accurate quantity of gel was weighed and then spreaded on the skin and after sometime scrapped the above gel from the skin and weighed. After subtracting the final amount of gel from the initial it was calculated that how much quantity of gel got spreaded on the skin and the result came after repeating the procedure for 3 times is given below.

F) pH Determination

After getting prepared Microsponge gel was evaluated for the pH. The pH of the gel was determined using digital pH meter of LABINDIA, India. The readings were taken for average of 3 times.

Table 6: Table revealing the results of Spredibility of microsponges

S. No.	Formulation code	Spredibility (mean ± S.D) n=3
1	M1	13.6 ± 0.89
2	M2	13.8 ± 0.91
3	M3	14.2 ± 0.81
4	M4	14.3 ± 1.03
5	M5	13.9 ± 0.98
6	M6	14.4 ± 0.77
7	M7	14.1 ± 0.93
8	M8	13.5 ± 0.85
9	M9	13.8 ± 0.84
10	M10	13.6 ± 0.91

Table 7: Table revealing the results of pH of the formulations

S. No.	Formulation code	pH (mean ± S.D) n=3
1	M1	6.9 ± 0.4
2	M2	6.5 ± 0.1
3	M3	7.1 ± 0.2
4	M4	7.0 ± 0.3
5	M5	7.4 ± 0.2
6	M6	7.4 ± 0.2
7	M7	7.2 ± 0.1
8	M8	6.9 ± 0.2
9	M9	7.4 ± 00.4
10	M10	7.3 ± 0.1

G) Viscosity measurement

The viscosity of the formulation was analysed by Brookfield viscometer with spindle no 7 at 50 rpm which revealed that with increase in polymer concentration the viscosity also increases.

H) *In vitro* diffusion studies using KC cell.

In vitro release studies was performed using KC cell diffusion apparatus at 37 °C. The release medium is selected, while considering solubility of active ingredients to ensure sink conditions. Sample aliquots were withdrawn from the medium and analyzed by the suitable analytical method at regular intervals of time. Egg membrane was fitted at the donor side of the cell and predetermined amount of formulation was mounted on the membrane. The receptor medium is continuously stirred at and thermostated with a circulating jacket. Samples are withdrawn at different time intervals and analyzed using suitable method of assay

Table 8: Table revealing the results of the analysed viscosity

S. No.	Formulation code	Viscosity (cps)
1	M1	2874
2	M2	2745
3	M3	2814
4	M4	2731
5	M5	2345
6	M6	2564
7	M7	2781
8	M8	2498
9	M9	2791
10	M10	2747

Table 9: Table revealing the results of Diffusion study of different formulations

S No.	Time (Hours)	Cumulative Release (%)									
		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
1	**1**	3.74	3.39	2.89	2.41	2.29	1.93	1.71	1.36	1.04	0.81
2	**2**	8.03	7.78	6.08	4.83	3.91	3.63	3.03	2.56	2.11	1.38
3	**3**	10.22	9.17	8.27	6.21	5.33	4.29	4.03	3.8	3.37	2.61
4	**4**	15.27	13.56	12.01	10.59	9.07	7.86	7.35	6.04	5.09	3.77
5	**5**	22.01	20.02	19.81	17.25	15.32	14.03	11.97	10.05	8.12	6.85
6	**24**	89.83	76.09	67.27	61.24	53.01	49.89	33.53	26.91	19.25	17.23

Table 10: Table revealing the comparison between results of different formulations.

S. No.	Formulation code	Percent Yield (%)	Drug Content	Particle Size (µm)	Cumulative Release (%)
1	M1	10.85	19.07	28.7	89.83
2	M2	12.96	27.82	29.8	76.09
3	M3	13.07	38.67	31.8	67.27
4	M4	15.06	74.03	33.7	69.24
5	M5	19.53	69.85	37.2	53.01
6	M6	26.21	63.02	31.3	49.89
7	M7	24.20	58.01	31.9	33.52
8	M8	30.60	51.06	29.4	26.91
9	M9	36.12	3705	27.5	13.25
10	M10	41.03	33.09	23.9	17.23

Table 11: Table revealing the results of Drug Release Kinetic Study

0	Mathematical models				Best fit Models
	Zero order	First order	Higuchi Model	Peppas Model	
	R^2	R^2	R^2	n	
M1	0.998	0.996	0.980	1.214	**Zero Order**
M2	0.996	0.979	0.982	1.157	**Zero Order**
M3	0.991	0.991	0.920	1.171	**Zero Order**
M4	0.992	0.981	0.911	1.177	**Zero Order**
M5	0.990	0.990	0.911	1.150	**Zero Order**
M6	0.980	0.980	0.918	1.106	**Zero Order**
M7	0.974	0.974	0.929	1.057	**Zero Order**
M8	0.970	0.970	0.935	1.023	**Zero Order**
M9	0.950	0.950	0.946	0.966	**Zero Order**
M10	0.960	0.961	0.932	0.943	**Zero Order**

Table 12: Table revealing the Interpretation of diffusional release mechanisms from polymeric films

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45 < n = 0.89	Non -Fickian transport
0.89	Case II transport
Higher than 0.89	Super case II transport

In kosmeyer peppas model the formulations mostly having the value of **n** greater than 0.89 so exhibit super case II transport.

4. Conclusion

The microsponges was prepared by quasi emulsion method and was evaluated for its different parameters which revealed many interesting results for efficient preparation of the microsponges. The formulation M6 have better results than other 9 formulations. **M6 have its particle size 31.3 ± 1.25 µm, percentage yield 26.21 ± 1.02 %, Drug content 63.02 ± 2.16 mg, Spreadability 14.4 ± 0.77, pH 7.4 ± 0.2, Viscosity 2564 cps, Cumulative Release 49.89 % in 24 hour,** all these parameters are in optimized range for preparing a controlled release dosage form so showing itself as an optimised formulation in this project work.

FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these microsponges. SEM photographs revealed the spherical nature of the microsponges in all variations. However, at higher ratios, drug crystals were observed on the microsponge surface. With the revealed results by different evaluation parameters, it is concluded that microsponges dug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost-effectiveness and efficacy of the therapy. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery.

Microsponge delivery systems can precisely control the release rates or target drugs to a specific body site have a vast impact on the health care system. A microsponge delivery system can release its active ingredient on a timer mode and also in response to other stimuli.

Therefore, microsponge has got a lot of potential and is a very emerging field which is needed to be explored. Microsponges constitute a significant part by virtue of their small size and efficient carrier characteristics.

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