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FORMULATION AND EVALUATION OF THE MICROSPONGES GEL FOR AN ANTI ACNE AGENT FOR THE TREATMENT OF ACNE

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ABSTRACT

Acne is a common inflammatory skin disease that mainly affects the face, neck, chest and upper back. Treatment depends on severity. Erythromycin has bacteriostatic activity which inhibits the growth of bacteria. They mainly act by binding to the 50s subunits of bacteria, 70s r-RNA complex, and protein synthesis. Erythromycin is also used topically to treat acne. They are used to treat moderate to severe inflammatory acnes or acne that isn't getting better with other treatments. Erythromycin works to treat acne by reducing the amount of acne causing bacteria called "propionibacteria" acnes on the skin, it also lessens inflammation and redness. Erythromycin is easily inactivated by the gastric environment and produce gastric disturbances such as diarrhoea, nausea, abdominal pain and vomiting. Erythromycin microsponges were prepared using quassi emulsion solvent diffusion method. Erythromycin microsponges were then incorporated into a Carbopol-940 gel prepared by hydrogel technique for release studies. The best formulation was found to be stable at room temperature for 3 months. Thus it was concluded that erythromycin can be formulated as microsponge gel that can release the drug upto 8hrs with reduced side effects.

Keywords: Acne, Erythromycin, Microsponges, Gel.

INTRODUCTION

In recent years it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress is drug therapy. A promising strategy involves the development of suitable drug carrier system. The *in -vivo* fate of the drug is not only determined by the properties of the drug, but it is also by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy.

Microsponges are porous spherical microparticles having a particle size range of 5-300 µm with a capability to entrap a wide range of active ingredients and are used as a carrier for topical drug delivery [1]. These microspheres act like microscopic sponges, storing the active drug until its release is triggered by application to the skin surface. The release of drug into the skin can be initiated by a various triggers like rubbing, concentration gradient, higher skin temperature, application of pressure [2] etc.

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed[3]. The Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Thus can significantly reduce the irritation of effective drugs without reducing their efficacy. Further these porous microspheres with active ingredients can be incorporated into formulations such as gels, creams, lotions and powders.

Microsponges consists of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner [3] which would be highly advantageous for irritant drug like benzoyl peroxide which would result in excellent efficacy with minimal irritation and to drugs which are to be released in a controlled manner so as to maintain the systemic concentration in a controlled manner.

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MATERIALS AND METHODS

Erythromycin was received as gift sample from Micro Labs pharmaceutical Pvt. Ltd. Bangalore (India), Ethyl cellulose, ethanol, methanol, dichloromethane, Carbopol 450, was obtained from SD fine chemicals Ltd., Mumbai (India). All other chemical and reagents were of analytical grade.

Incorporation of erythromycin microsponges into gel

To obtain a suitable topical formulation for application, microsponges were incorporated into a gel base. After the preliminary tests for the selection of suitable polymer for gel, carbopol was found to be ideal. Carbopol was soaked overnight in minimum quantity of water and allowed to swell up. Erythromycin microsponges equivalent to 0.05 % w/w of drug were dispersed into the gel base. Permeation enhancer was also added. The pH was adjusted with triethanolamine which resulted in a translucent gel [4].

Formulations with varying concentration of Carbopol

To obtain the most satisfactory product, four gel formulations were prepared using carbopol in the concentration range of 0.5% to 2%. Gel formulation were coded as $G_1 - G_4$ and were evaluated for their physical appearance and consistency the results were reported.

Incorporation of permeation enhancer into Gel formulations

In order to investigate the effect of permeation enhancer on the permeation characteristics of erythromycin via the barriers different gel formulations coded as $G_5 - G_{10}$ were prepared containing different permeation enhancer. Gel formulation G_4 was used for this study.

EVALUATION OF GEL FORMULATIONS

Homogeneity

The prepared gels were visually inspected for clarity, colour and transparency. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness [5].

pH of the gels

The pH of gel was determined after diluting and dispersing it in distilled water using digital pH meter [6].

Spreadability

Spreadability was determined by glass slides and a wooden block, which was provided by a pulley at one end. By this method, spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground glass slide was fixed on this block. An excess of gel (about 1gm) of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 20gms, lesser the time taken for separation of two slides better the Spreadability [6].

Spreadability was then calculated using the following formula: $S = M \times L / T$

Where, S = is the spreadability,

M = is the weight in the pan (tied to the upper slide),

L = is the length moved by the glass slide

T = represents the time taken to separate the slide completely from each other.

Extrudability Study

It is a usual empirical test to measure the force required to extrude the material from tube. Consist of a wooden block inclined at an angle of 45^0 fitted with a thin metal strip at one end. While the other end was free. The aluminium collapsible tube containing 10gm of gel was positioned on inclined surface of wooden block; 30gm weight was placed on free end of the aluminium strip and was just touched for 10 sec. The quantity of gel extruded from each tube was noted. More quantity extruded better was extrudability. The measurement of extrudability of each formulation was tabulated [6].

Viscosity

The viscosity of the different gel formulations was determined using a Brookfield viscometer with spindle no 7 at 50 rpm [6].

Drug content

1gm of erythromycin gel was accurately weighed dissolved using methanol, sonicated for a period of 10-15mins and made up to the mark in 100 ml volumetric flask with methanol. From this 10 ml was pipetted out and diluted to 100 ml with methanol and the final dilution was made using distilled water to get a concentration within Beer's range. The absorbance was measured spectrophotometrically at 264 nm against blank gel treated in the same manner as sample.

In-vitro permeation studies of gel formulations

In-vitro studies of the gel were carried out across the egg membrane extracted by using the concentrated Hcl.. The receptor compartments were filled with phosphate buffered saline (PBS) pH 6.8, Study was carried out using excised egg membrane. The entire setup was placed on a thermostatic magnetic stirrer and the temperature was maintained at 37^0C throughout the study.Permeability studies were carried out over a period of 8 hrs at regular intervals. Samples were withdrawn and analyzed spectrophotometrically at 264 nm.

Kinetics of drug release

To examine the drug release kinetics and

mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Stability Studies

The prepared final formulation G_{10} was transferred to collapsible aluminum tube which was stored at room temperature. Testing was carried out at 0, 1, 2 and 3 months respectively. Physical appearance, pH, spreadability, extrudability, *in-vitro* release and drug content were tested accordingly [7-10].

RESULTS

Fig 1. Invitro Gel release studies

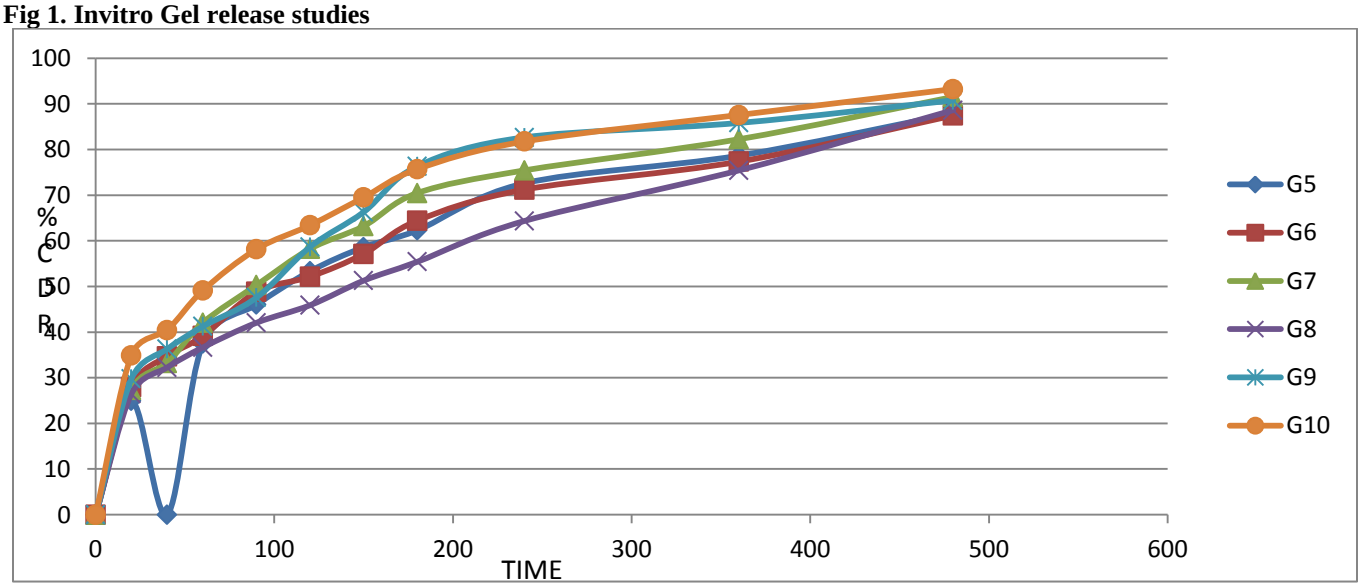

Fig 2. Release kinetics profile of Erythromycin microsponges gels according to zero order

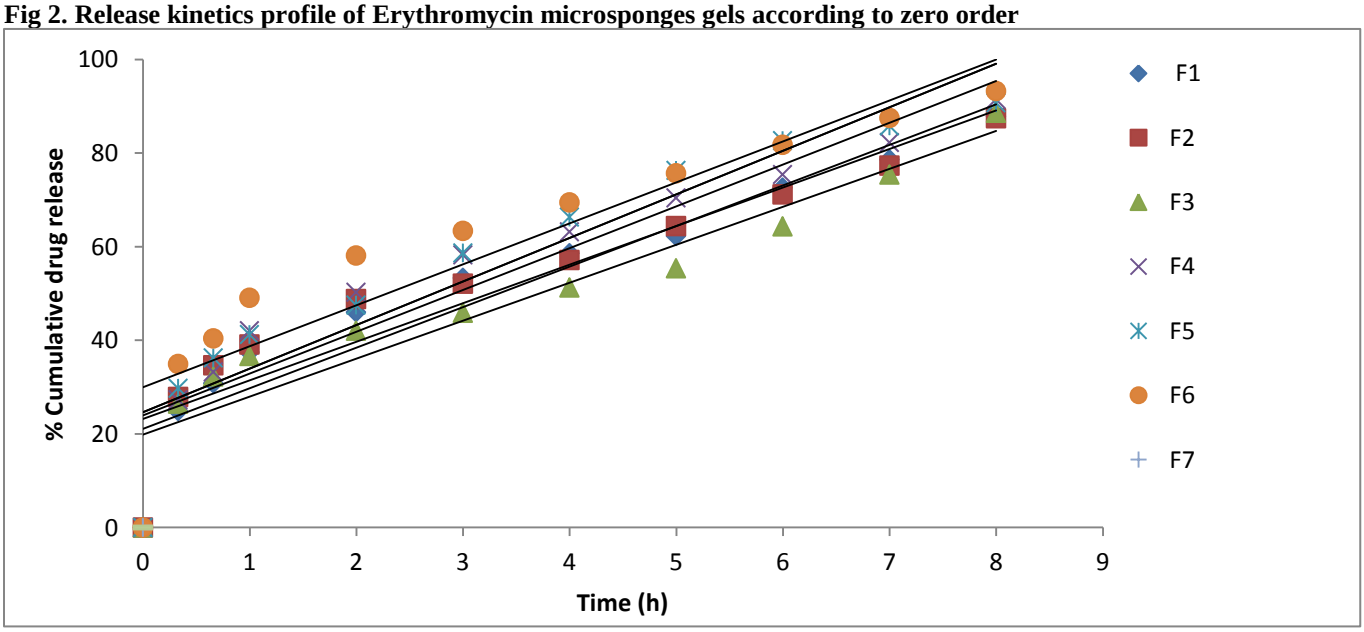

Fig 3. Release kinetics profile of Erythromycin microsponges gels according to first order

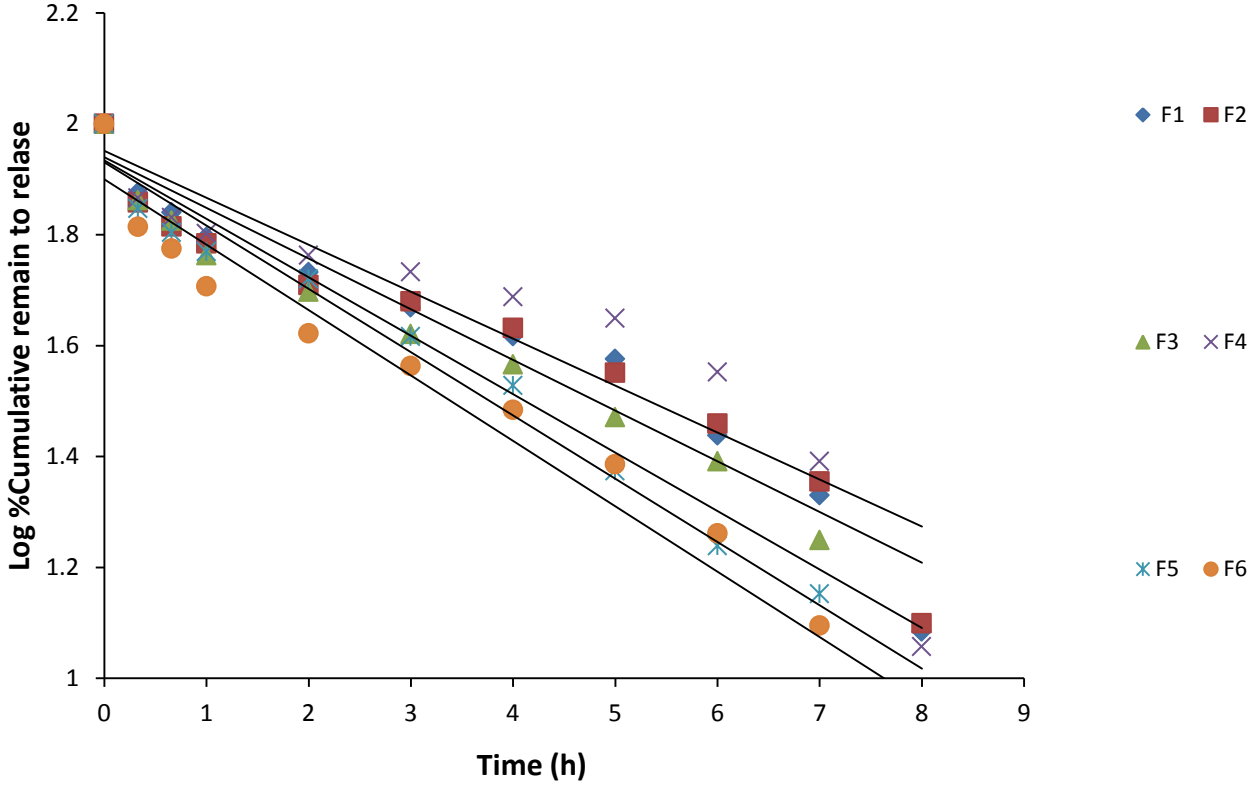

Fig 4. Release kinetics profile of Erythromycin microsponges gel according to Higuchi matrix diffusion

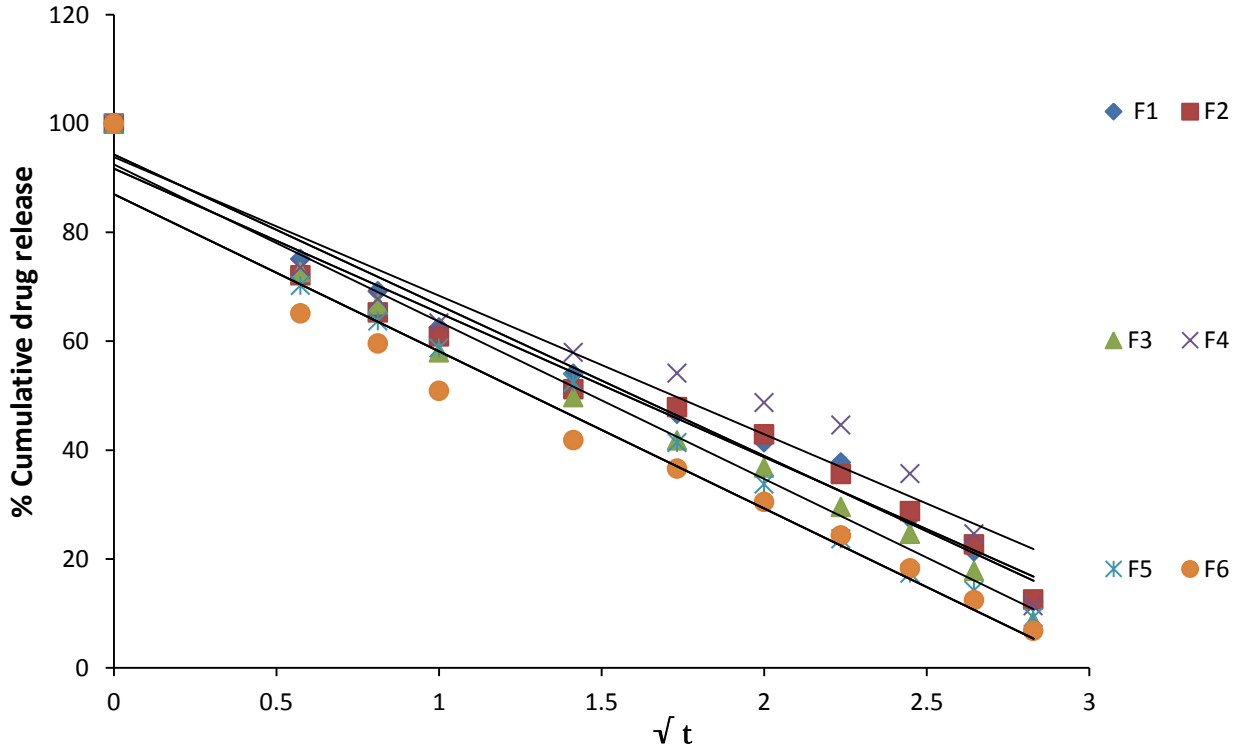

Fig 5. Release kinetics profile of Erythromycin microsponges gel according to Peppas model

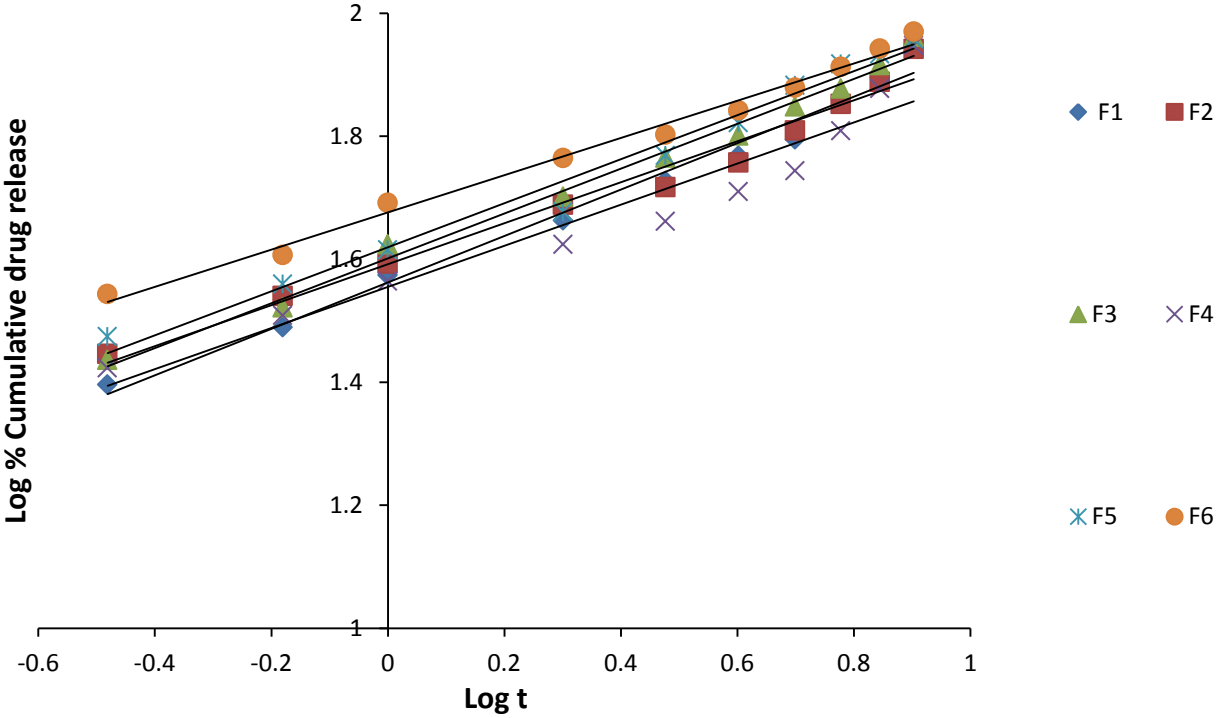

Fig 6. *In-vitro* release studies of gel formulation G_{10} after stability studies

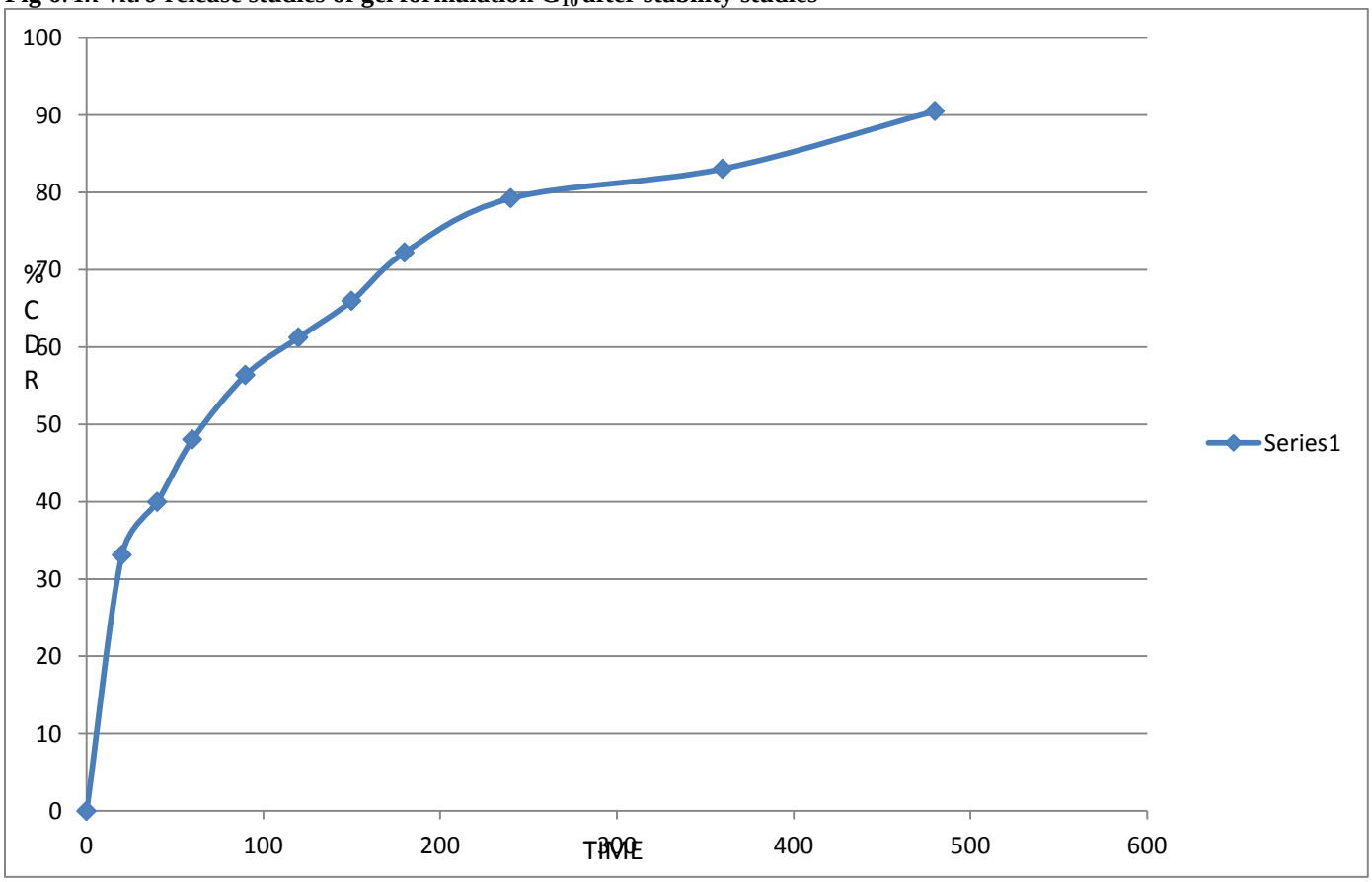

Table 1. Physical evaluation of Carbopol 940 gel formulations

Formulations	Carbopol 940 Concentration(%)	Triethanolamine (w/v)	Erythromycin (w/w)	Appearance
G1	0.5	0.5%	0.05 %	Non Transparent gel, Leakey consistency
G2	1.0	0.5%	0.05 %	Non transparent gel, Leakey consistency
G3	1.5	0.5%	0.05 %	Non transparent gel Leakey consistency
G4	2	0.5%	0.05 %	Non transparent thick gel

Table 2. Gel formulations containing different permeation enhancers

Formulations	Carbopol (%)	Propylene glycol(%v/w)	Isopropyl Myristate (% v/w)	Ethanol (%v/w)
G5	2	-	1	5
G6	2	7.5	2	5
G7	2	7.5	3	5
G8	2	7.5	4	5
G9	2	7.5	5	5
G10	2	7.5	6	10

Table 3. Evaluation of Microsponge incorporated gels

Sl. No	Formulations	P^H	Spreadability (gm.cm/sec)	Homogeneity	Viscosity (cps)	Extrudability	Drug content (%)
1	G5	6.63	11.28	**	3970	**	83.17
2	G6	7.1	11.64	**	4105	**	80.06
3	G7	6.82	11.96	**	3680	**	78.41
4	G8	6.79	12.56	**	4281	**	82.5
5	G9	7.2	12.81	**	3462	**	79.16
6	G10	6.71	13.33	**	4018	**	83.79

** denotes good

Table 4. *In-vitro* release studies of gels containing permeation enhancer

Sl. No	Time (min)	%CPR±S.D					
		G5	G6	G7	G8	G9	G10
1	0	0	0	0	0	0	0
2	20	24.9±2.20	27.91±2.10	27.29±2.13	26.47±2.09	29.76±2.17	34.91±2.15
3	40	30. 8±2.46	34.68±2.53	33.23±2.54	32.24±2.57	36.27±2.56	40.41±2.46
4	60	37.47±2.78	39.13±2.76	42.04±2.65	36.64±2.62	41.24±2.63	49.12±2.73
5	90	46.01±2.97	48.80±2.98	50.28±2.86	42.04±2.86	47.55±2.89	58.15±2.93
6	120	53.33±3.15	52.13±3.43	58.23±2.47	45.88±3.42	58.66±3.56	63.40±3.43
7	150	58.59±3.50	57.13±3.66	63.21±2.38	51.27±3.56	66.29±3.92	69.50±3.56
8	180	62.29±3.87	64.41±3.89	70.45±3.86	55.39±3.89	76.33±4.02	75.69±3.97
9	240	72.59±4.18	71.21±4.23	75.42±4.17	64.34±4.15	82.65±4.16	81.75±4.19
10	360	78.64±4.39	77.33±4.56	82.24±4.69	75.41±4.70	85.81±4.35	87.55±4.32
11	480	87.87±4.96	87.44±4.78	91.51±4.69	88.61±4.83	90.76±4.84	93.23±4.8

Table 5. Regression co-efficient (r^2) values of different kinetic models and diffusion exponent (n) of Peppas model for Erythromycin microsponges gel

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2 value	'n' value
F1	0.9030	0.9451	0.9822	0.9857	0.3772
F2	0.8778	0.9335	0.9687	0.9757	0.3331
F3	0.8828	0.9406	0.9820	0.9907	0.3641
F4	0.8929	0.8569	0.9379	0.9224	0.3344
F5	0.8869	0.9820	0.9832	0.9817	0.3580
F6	0.8272	0.9553	0.9597	0.9903	0.3025

Table 6. Stability studies of final formulation G_{10}

Sl. No	Sampling interval	Homo geneity	pH	%Drug content*	Spreadability (gm.cm/sec)	Viscosity (cps)	Extrudability
1	Initial	**	6.70	83.72±0.12	13.32	4016	**
2	1 month	**	6.64	83.62±0.34	13.26	4014	**
3	2 months	**	6.62	82.78±0.12	13.23	4010	**
4	3 months	**	6.6	82.56±0.37	13.18	4006	**

*Average of six determinations

Table 7. *In-vitro* release studies of gel formulation G_{10} after stability studies

Sl. No	Time in min	%CPR±SD
1	0	0
2	20	33.10±2.12
3	40	39.97±2.38
4	60	48.06±2.56
5	90	56.38±2.89
6	120	61.24±3.06
7	150	65.98±3.18
8	180	72.91±3.56
9	240	79.24±3.97
10	360	83.06±4.34
11	480	90.52±4.82

*Average of six determination

CONCLUSION

The present study was to design, develop, and evaluate the microsponge incorporated gel for topical sustained drug delivery of erythromycin for extended release. Erythromycin is easily inactivated by the gastric environment and produce gastric disturbences such as diarhoea, nausea, abdominal pain and vomiting. The best formulation F_{18} was incorporated into gels and gels were evaluated for physical parameters and showed extended release upto 8 hrs.

Analysis of drug release mechanism showed that the drug release followed Fickian Diffusion and the best fitted model was found to be Peppas

Stability studies at room temperature revealed that there was no noticeable change in the homogeneity, pH, spreadability, extrudability, viscosity, drug content and *in-vitro* release at the end of three months.

Thus it was concluded that the selected anti-acne drug can be developed into microsponges and further can be incorporated into gel for topical application.

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