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Formulation and Evaluation of Gel-Loaded Microsponges of Roxithromycin for Topical Drug Delivery

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Abstract: In this study Eudragit RL 100 facilitated microsponges were prepared by the double emulsification technique (Quasi emulsion technique) and subsequently dispersed in a carbopol gel base for controlled delivery of roxithromycin to the skin. The microsponges formulations were prepared by quasiemulsion solvent diffusion method employing Eudragit RL 100 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 content and encapsulation 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 101.8 to 136.3μm. 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 1:5) increased their yield (57.00 to 91.82), average particle size of all formulations ranges from 110μm to 120μm 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 6.3 ± 0.2, The viscosity of the formulation was analysed by Brookfield viscometer with maximum reading of 2024 and minimum reading of 1970 cps, the drug content of different formulations was found in the range 95.2 to 99.8%, the spredibility of gel containing microsponges revealed in the range of 17.4 to 25.10 showing good characteristics of spreading, the cumulative release of the formulations are in the range of 61.1% to 75.4%%.

Keywords: Microsponges, Roxithromycin, Eudragit RL 100, Sustained and controlled release, Scanning Electron Microscopy (SEM)

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I. 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(1). 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 microsponges are colloidal in nature which act as carriers, they can solubilize poorly drug and provide enhances drug release because of the mode of entrapment of drug by carrier system leads to the particle size reduction of drug, thereby increases the dissolution rate and also improved drug's bioavailability and in some case modifying its pharmacokinetics parameters(2). Microsponge are tiny, spherical, uniform and micropous polymeric beads. The size of microparticles are in the range of 5-300μ. The microsponges have interconnected voids and wide system of porous nature holds an active agent to provides the controlled release of it. This delivery system possesses a flexibility to load a variety of actives including anti-infective, emollients, fragrances, various essential oils and sunscreen(3). Providing the benefit of enhanced product effectiveness, tolerability, extended wear and mildness in skin therapy. The release of active ingredient occur in controlled way due to the spongy surface of microsponge. 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 (4). The proposed work involves Formulation and evaluation of gel-loaded microsponges of roxithromycin for topical delivery by Eudragit RL 100 as polymer by quasi emulsion process. And finally the optimized roxithromycin 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 [(5)].

II. MATERIALS AND METHODS

Roxithromycin is a gift sample from Alembic Ltd, baddi. Eudragit RL 100, Polyvinyalcohol and Carbopol 980, Dicholromethane & triethanolamine were used from Govt. College of pharmacy rohru.

2.1 Method of Preparation of Microsponge:

Microsponges of roxithromycin and Eudragit RL 100 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[(6,7)]. Table no 1 gives the detailed information about the prepared formulations.

1. **Preparation of internal phase:** the phase was consisted of drug (roxithromycin), polymer (Eudragit RL 100) and solvent (ethanol and dichloromethane in ratio 1:1). To prepare this phase, Eudragit RL 100) and solvent (ethanol and dichloromethane in ratio 1:1). To prepare this phase, Eudragit RL 100 was dissolved in the mixture of solvents and then drug was further added to it and dissolved under under sonnication.
2. **Preparation of external phase (aqueous phase):** for the preparation of aqueous phase, weighed quantity of polyvinyl alcohol was taken and dissolved in 50ml of water in beaker.
3. **Mixing:** The internal organic phase was poured into the external aqueous phase by drop wise.
4. **Stirring:** The stirring was continued up to 6 hrs till the insoluble, rigid microparticles i.e. microsponges is formed.
5. **Filtration:** The mixture was allowed to stir until the foam settled down and after the complete evaporation of dichloromethane the mixture was filtered with whatmann filter paper (0.45 µm).
6. **Drying:** The microsponges were then dried in an air heated oven.

S. No.	Ingredient (mg/ml/gm)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Roxithromycin: Eudragit RL 100	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3	1:3.5	1:4	1:4.5	1:5
2.	Roxithromycin (mg)	100	100	100	100	100	100	100	100	100	100
3.	Eudragit RL 100 (mg)	50	100	150	200	250	300	350	400	450	500
4.	Dicholromethane:Ethanol (5ml)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
5.	Polyvinyalcohol (mg)	500	500	400	300	300	200	100	100	100	100
6.	Distilled water (ml)	50	50	50	50	50	50	50	50	50	50

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

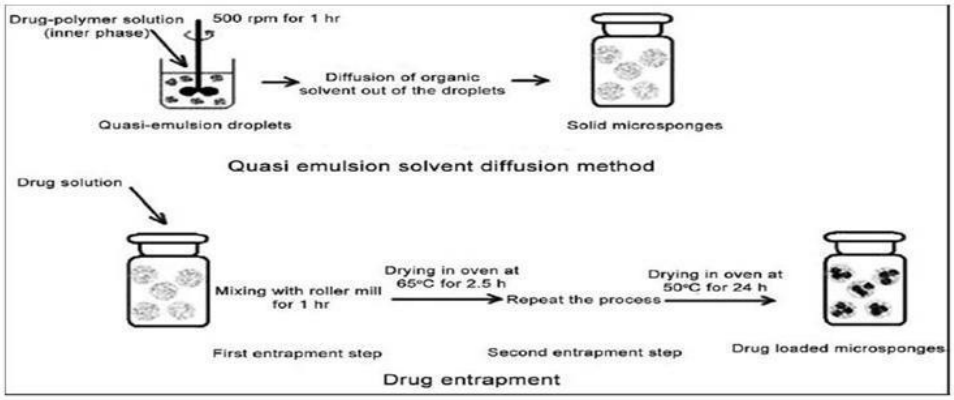

Fig 1: Image Showing Quasi-emulsion solvent diffusion method set up.

The prepared microsponges were further evaluated for various parameter such as physical appearance or morphology, topography, particle size, production yield, drug content, loading efficiency, in vitro diffusion studies etc[(8,9)].

2.2 Preparation of Carbopol Gel.

Gel from different formulae were prepared using varying concentration of carbopol 940 as gelling agent and other excipients as shown in table 2 [(10)].

S No.	Ingredient	Quantity (mg/ml)				
	Formulation code	G1	G2	G3	G4	G5
1.	Carbopol 980	0.55	1%	1.5%	2%	3%
2.	Sorbitol (ml)	1	2	2.5	3	3.5
3.	Methyl paraben (g)	0.1	0.1	0.1	0.1	0.1
4.	Alcohol (ml)	1	2	2	2	4
5.	Triethanolamine (ml)	1	1.5	2	2	3
6.	Distilled water	q.s	q.s	q.s	q.s	q.s

Table 2: Table revealing the master formula for gel formulation

On the basis of evaluation of gel one formulation was optimized. In optimized formulation microsponges of roxithromycin were added.

1. A clear dispersion of carbopol 980 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), sorbitol and ethanol was added to resist the microbial growth.
3. The final wieght is adjusted 10ml volume was maintained with water. Gel prepared were degassed with ultrasonication.

2.3 preparation of Roxithromycin microsponges loaded gel

Gel of roxithromycin microsponge formulations (F3, F4, and F5) named GM1, GM2 AND GM3 respectively were prepared by using the formula G4 of carbopol gel as it was found optimized from the evaluated parameters[(11)]. The formula for the preparation of microsponges gel is shown in the table 3.

S.No	Formulation ingredients	Equivalent to 1% w/w of Roxithromycin concentration		
		GM1	GM2	GM3
1.	Roxithromycin Microsponges	254.45 mg	343 mg	497 mg
2.	Carbopol 980	2%	2%	2%
3.	Sorbitol (ml)	3.0	3.0	3.0
4.	Triethanolamine (ml)	2.0	2.0	2.0
5.	Methyl paraben (g)	0.1	0.1	0.1
6.	Alcohol	2.0	2.0	2.0
7.	Distilled water	q.s	q.s	q.s

Table 3: Table revealing the master formula for roxithromycin microsponges loaded gel

The prepared gel - loaded microsponges of roxithromycin was evaluated for various parameter such as; physical appearance, p^H, Drug content, viscosity, spreadibility, in vitro diffusion study, data analysis by using release model etc [(12)].

III. EVALUATION RESULTS OF MICROSPONGES

3.1 Morphology and Surface Topography:

The morphological evaluation is done by visual inspection (student's microscope) and from the SEM images of formed microsponges as well as fractured microsponges to illustrate its ultra structure are shown in the figure no. 2.

Figure no.2 SEM images of roxithromycin microsponges

Figure no.3 SEM images of fractured roxithromycin microsponges

Physical appearance showed white to almost white microsponge particles were obtained by quasi emulsion solvent diffusion method. The images obtained from SEM revealed that the particles were spherical in shape with porous structure which indicates that microsponge formulations were properly prepared. Fractured images showed that due to evaporation of solvent from the surface of microsponges pores were induced.

3.2 particle size analysis:

Particles size analysis of microsponges is shown in table no.4

Sr. No.	Formulation code	Particles size (µm)
1	F1	101.8
2	F2	105.4
3	F3	107
4	F4	112.3
5	F5	110.5
6	F6	115
7	F7	118.4
8	F8	120.6
9	F9	131.3
10	F10	136.3

Table 4: Table revealing the results of particles size analysis

The particles size revealed that particles size had increased with increase in drug: polymer ratio. This may be due the reason, because of higher drug: polymer ratio, polymer available was in more quantity thereby increased the wall thickness which led to increase in size of microsponges.

3.3 production yield:

The production yield is to be shown in the table 5 which was found to be increase with the increase in the amount of drug to polymer ratio.

Sr. No.	Formulation code	Production yield (%)
1	F1	57.00
2	F2	64.44
3	F3	73.30
4	F4	82.04
5	F5	83.26
6	F6	85.46
7	F7	82.56
8	F8	91.82
9	F9	83.40
10	F10	86.07

Table 5: Table revealing the results of production yield

The production yield of all batches of microsponges ranged from 60% to 90% from drug polymer ratio 1:1 to 1:4 i.e. from F1to F8, and then further found to be decreased from drug: polymer ratio 1:4.5 to 1:5 i.e. F9 and F10.with further higher drug: polymer ratio, higher the production yield found. Further, with low concentration of PVA, production yield also found to be decreased in series of the formulations. Due to the presence of high polymer amount, the inner viscosity may get increased, and the time required for the diffusion of dichloromethane takes more time for the formation of droplets which improves the production yield.

3.4 Drug content and encapsulation efficiency:

Drug content and encapsulation efficiency of efficiency of microsponges formulation is shown in table 6 was found to be lesser than theoretical value for every drug: polymer ratio: The drug content of formulation was found to be decrease with increase in drug to polymer ratio while encapsulation efficiency reflect that with the higher drug: polymer ratio, greater drug loading up to certain limit (F6) occurred and then decreased further from F7 to F10. The decrease in content of the formulation is due to the fact of either solubilisation of drug in good solvent of evaporation of the actives while processing in formulation of microsponges and reason behind encapsulation efficiency is that. Initially the polymer (PVA) was sufficiently available to encapsulate the drug but with decease in PVA availability decrease the viscosity of dispersion phase as compared to the higher drug: polymer ratio thus encapsulation found to increase up to certain limit and then decease as shown in table no. 6.

S.No.	Formulation code	Drug content (%) Mean + SD) N=3	Encapsulation efficiency (%)
1	F1	56 ± 0.30	85.4 ± 0.011
2	F2	38.4 ± 0.20	78.2 ± 0.020
3	F3	37.2 ± 0.04	97.3 ± 0.042
4	F4	29.7 ± 0.05	88.1 ± 0.061
5	F5	22.5 ± 0.04	89.0 ± 0.023
6	F6	23.0 ± 0.03	57.0 ± 0.043
7	F7	13.0 ± 0.4	55.0 ± 0.076
8	F8	12.0 ± 0.35	56 ± 0.098
9	F9	8.3 ± 0.24	56 ± 0.087
10	F10	8.1 ± 0.14	55 ± 0.054

Table 6: Table revealing the results of drug content & encapsulation efficiency

3.5 In- vitro diffusion release:

The in –vitro release of all the formulation is shown in table 7 the drug release was observed to decline within a range of 87% to 44% with respect to rise in drug to polymer ratio from 1:0.5 to 1:5. This is because of the fact that due to high polymer amount thickening of polymer matrix wall results in extended diffusion and thus lead to lesser drug release. The highest drug release was found to be in the F1 which is 87% at ratio 1:0.5 while the lowest 44% for F10 at ratio 1:5 higher release in the initial formulation F1 and F3 may be due to less polymer matrix or may be due to non- encapsulated drug at lower drug to polymer ratio as shown in table no. 7.

Time (min)	Cumulative percent release (% CPR)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0
60	16.7	11.8	10.2	5.1	10	7.4	0	0	0	0
90	25.8	15.3	12.9	12	17.70	15.6	12.6	12.7	19.5	13.6
120	34.3	26.9	22.9	22.6	25.50	26.7	14.7	14.9	22.5	19.4
180	43.7	38.7	35.08	29.93	35.90	38.4	28.5	35.8	27.3	21.9
240	52.8	45.6	43.33	42.38	49.0	46.78	34.7	42.8	29.5	27.18
300	63.12	56.1	60.05	55.13	59.80	57.14	39.8	43.7	35.14	28.5
360	77.03	67.5	69.18	59.42	68.30	63.55	47.35	46.8	44.6	31.15
420	84.3	81.2	79.20	74.18	79.0	73.28	57.59	52.4	45.9	36.7
480	87	86.4	82.90	83.80	82.90	74.53	64.47	57.3	50.8	44

Table 7: Table revealing the results of diffusion study of different formulations

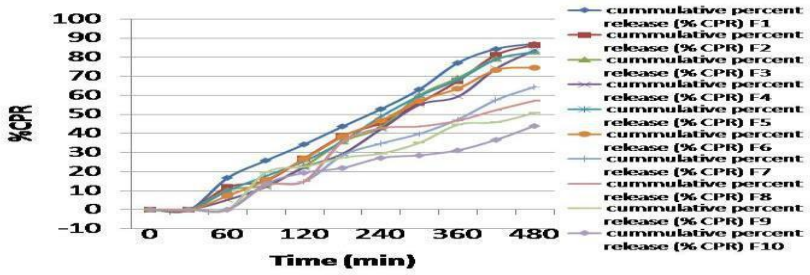

Figure no. 4 in vitro diffusion release of formulation F1 TO F10

3.6 Optimized formulation of Microsponges by its parameter of evaluation:

The selection of batches were based on superiority of parameters evaluated for all the different formulations of microsponges having good production yield, drug content, higher encapsulation efficiency and optimum in vitro release of microsponges shown in table 4,5,6,7 etc. On the basis of evaluation of microsponges, the optimized batches for the gel formulation of roxithromycin microsponges were found to be F3 , F4 and F5 having encapsulation efficiency of 97.3% , 88.1% ``and 89%, production yield in range of 73 to 83% and optimum release of about 80%.

3.7 Data analysis of microsponges formulation:

The data of dissolution data obtained from optimized formulation F3, F4 and F5 was done using zero order, first order, higuchi square root of time and korsmeyer- peppas models. the regression coefficients (R^2) were calculated and represented in table 8. The in vitro release data were subjected to release model showed the highest regression value for the Higuchi square root model. Thus, on the basis of maximum regression value, Higuchi square root was found to be best fit model for the optimized formulation of microsponges.

Formulation code	Zero order		First order		Higuchi square root		Korsmeyer-peppas		Best fit model
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	
F3	0.988	0.188	0.974	0.001	0.921	10.12	0.814	1.886	Zero order
F4	0.992	0.180	0.945	0.001	0.911	9.60	0.800	1.895	Zero order
F5	0.985	0.185	0.983	0.001	0.940	9.90	0.815	1.895	Zero order

Table 8: Table revealing the results of drug release kinetics study

3.8 Optmized formulation of gel by parameter of evaluation:

The selection of optimized gel was done on the basis of various evaluation parameters of different gels. The gel without medication was formed with varying concentration of carbopol, solvents and other excipients. The evaluation parameters of gel G1, G2, G3, G4 and G5 are shown in table 9 the gel of selected formulation F3, F4 and F5 was made by utilizing the formula G4 Containing carbopol 980 in 2% concentrations.

Parameters	G1 (0.5%)	G2 (1%)	G3 (1.5%)	G4 (2%)	G5 (3%)
Color	Transparent	Transparent	Transparent	Transparent	Transparent
After feel effects	Smooth	Smooth	Smooth	Smooth	Sticky
Consistency	Easy pourable	less	Good	Very good	High
Homogeneity	Good	Good	Good	Good	Good
pH	6.0	6.1	6.3	6.3	6.6
Spreadability	Very high	high	high	Good	Less
Viscosity	Less	Less	Good	Good	High

Table no.9: Table revealing the result of evaluation of gel

3.9 Evaluation of roxithromycin microsponges gel:

The prepared gels of formulation F3, F4 and F5 named GM1, GM2 and GM3 were evaluated for the visual inspection for color, texture and appearance, consistency of gel, p^H of the formulation, homogeneity, drug content, spreadibility and viscosity. The parameter evaluated are shown in the table 10.

Parameter	Pure gel	GM1	GM2	GM3
Carbopol strength	2.5%	2.5%	2.5%	2.2%
Color	Transparent	Transparent	Transparent	Transparent
After feel effects	Smooth	Smooth	Smooth	Slightly rough
Consistency	Good	Good	Good	Residue remaining
Homogeneity	Good	Good	Good	Good
p^H Determination	6.3	6.3	6.4	6.4
Drug content	99.7%	97.6%	96.4%	95.3%
Spreadability	25.10	22.9	20.10	17.4
Viscosity (cps)	1970	2015	2024	1986

Table no.10: Table revealing the result of evaluation of roxithromycin microsponges gel.

3.10 In vitro diffusion study of roxithromycin microsponges gel formulations:

The release of microsponges gel formulation is shown in table 11. It was found that the conventional gel released their 95% of the drug in 4 hours while the microsponges gel released about 61% to 75.4% of drug in 8 hours.

Time (min)	Cumulative percent release (% CPR)			
	Pure gel	GM1	GM2	GM3
0	0	0	0	0
30	20.1	10.05	12.4	7.6
60	31.4	15.74	19.8	10.4
90	42.9	19.3	27.2	15.6
120	64.5	26.38	32.9	26.2
180	83.15	32.84	42.5	36.98
240	94.6	40.9	50.2	47.7
300	-	45.52	58.19	56.0
360	-	51.8	66.2	64.1
420	-	56.7	72.6	68.2
480	-	61.1	75.4	71.9

Table no.11: Table revealing In vitro diffusion study of roxithromycin microsponges gel

The in vitro release of the Gel GM1 was found 61.1% only, GM2 75.4% and GM3 released 71.9% of drug. The release of the drug from formulations showed GM1 released the drug in confined manner while Gel GM2 and GM3 showed the better release profile as shown in figure 5.

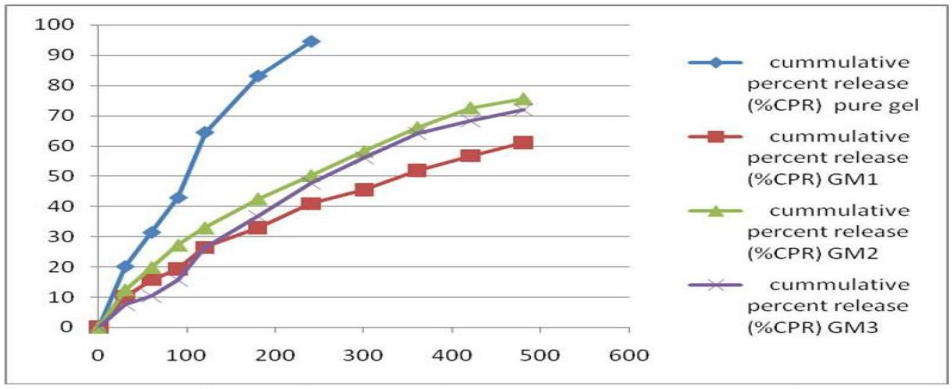

Figure 5: in vitro diffusion release of formulation of pure gel, GM1,GM2 & GM3

3.11 Data analysis:

The data analysis of dissolution data obtained from pure roxithromycin gel and selected formulations GM1, GM2 and GM3 was done using zero order, first order, higuchi square root of time and korsmeyer - peppas models. The regression coefficient (R^2) were calculated and represented in table12.

Formulation code	Zero order		First order		Higuchi square root		Korsmeyer peppas		Best fit model
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	
roxithromycin Gel	0.970	0.397	0.954	0.005	0.995	14.58	0.997		Korsmeyer – peppas
GM1	0.966	0.120	0.994	0.001	0.987	6.76	0.999		Korsmeyer – peppas
GM2	0.961	0.150	0.996	0.001	0.988	8.45	0.998		Korsmeyer – peppas
GM3	0.973	0.156	0.995	0.001	0.951	8.56	0.975		First order

Table no.11: Table revealing the results of drug release kinetics study

The in vitro release data of gel were subjected to release model showed the highest regression value for the korsmeyer- peppas model for pure Gel, Gel, GM1 and GM2 and first order model for gel GM3. Thus on the basis of maximum regression value , korsmeyer- peppas was found to be best fit model for the Gel GM1 and GM2 which showed the release of microsponges gel were sustained release. The best gel form the various gel formulation was found to be GM2 in all respect having good transparency and consistency, better smoothness, excellent after feel effect with no residual particles, good in vitro release of 75.4% for about 8 hours, optimum skin p^H 6.4, Spreadability (20.1), viscosity (2024) and best fit model of sustained release i.e. korsmeyer peppas

IV. 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 F3, F4 and F5 have better results than other 7 formulations. F3,F4 and F5 having encapsulation efficiency of 98%, 88 and 89%, production yield in range of 73 to 83% and optimum release rate of about 80%. All these parameters are in optimized range for preparing a controlled release dosage form so showing itself as an optimised formulation in this research 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 drug 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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