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Formulation And Evaluation Of Topical Gel Loaded With Ibuprofen Microsponges.

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ABSTRACT

Novel microsponges were designed as carriers for topical delivery of Ibuprofen which minimized its gastro intestinal side effects and provided consistent drug levels at application site for longer period of time. Microsponges were developed using novel quassi emulsion solvent diffusion method using different drug: polymer ratios. The batch F3 showed optimum loading efficiency, entrapment efficiency and maximum drug release upto 8 hours, associated with burst effect. Optimized microsponges were incorporated into gel prepared with different polymer concentrations. The gel formulations were evaluated for % drug content, pH, viscosity, spreadability and *in vitro* diffusion study. The properties of microsponges were greatly affected by drug: polymer ratio. Drug loading, entrapment efficiency, production yield was found to increase with increase in drug: polymer ratio while a decrease in particle size was observed. A controlled release topical drug delivery of Ibuprofen developed as a microsponge loaded gel offers solubilizing matrix for the drug, served as a local depot for controlled drug release and provided a rate limiting matrix barrier for modulation of drug release. The designed microsponge gel may be evaluated in vivo to confirm its extended release. (1)

KEYWORDS: Microsponges, Quassi emulsion solvent diffusion, Ibuprofen, anti-inflammatory, Eudragit RS100.

INTRODUCTION:

One of the biggest challenge faced by pharmaceutical scientist is to control the delivery rate of active ingredients to a predetermined site in human body. Several systems under transdermal delivery systems (TDS) can be used for systemic delivery of drugs using the skin as a portal of entry. But TDS is not practicable for delivery of materials whose final target is skin itself. Controlled release of drug onto the epidermis with assurance that drug remains primarily localized and does not enter the systemic circulation in significant amounts is a challenging area of research(1)

No efficient vehicles have been developed for controlled and localized delivery of drug into the stratum corneum and the under lying skin layers and beyond the epidermis[2]. Application of topical drug suffers many problems. Ointments, which are often aesthetically unappealing faces the problem like greasiness, stickiness and often result in lack of patient compliance. These vehicles require high concentration of active agents for effective therapy because of the low efficiency of delivery system. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drug with vehicle. Thus the need exist for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing it's transdermal penetration into the body. The microsponge delivery system fulfillls this requirement. (1)

The microsponge delivery system (MDS) is a patented polymeric system consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, anti-infective, anti-fungal and anti-inflammatory agents. It can be a rigid structure, hard as a piece of ceramic, or soft as a bathroom sponge depending on the polymer composition, degree of cross-linking and on the parameters necessary to achieve the desired rate of release of active materials from the pores.(2)

They have particle size in the range of 300-500µm. Depending upon the size, the total pore length may range upto 1ft and the pore volume upto 1ml/g. when applied to the skin the microsponge drug delivery system releases its active ingredient on a time mode and also in response to other stimuli such as rubbing, temperature and pH. Microsponges have the capacity to adsorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives upto three times its weight differentiates microsponges from other types of dermatological delivery systems.

Gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent .when dispersed in an appropriate solvent,gelling agents merge or entangle to form a three dimensional colloidal network structure. This network limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel's resistance to deformation and, therefore its viscoelastic properties.

Ibuprofen is non-steroidal anti-inflammatory drug often used in the treatment of mild to moderate pain and inflammatory conditions such as ankylosing spondilitis, osteoarthritis, rheumatoid arthritis. It is selective inhibitor of cycloxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. It's pharmacological effects are believed to be due to inhibition of cycloxygenase (COX) which decreases the synthesis of prostaglandins involved in mediating inflamamation, pain and fever. Antipyretic effects may be due to action on hypothalamus, resulting in an increased in flow, vasodialation and subsequent heat dessipation.

It has pH dependent solubility and permeability. The drug has a half-life of 1 to 2 hours. Because of its short biological half-life the drug has to be administered frequently. Furthermore oral Ibuprofen causes irritation in gastric mucosal membrane and possess a bitter taste and after taste. Therefore In this study novel microsponges were prepared as carriers for topical delivery of Ibuprofen which minimizes its gastro intestinal side effects and provides consistent drug levels at application site for longer period of time.

MATERIALS AND METHODS

Material:

Ibuprofen was provided as a gift sample from Shasun Pharmaceuticals, Ltd. Chennai. Eudragit RS 100, Carbopol 940 was bought from Research lab, Mumbai. PVA, Dichloromethane, Methanol, Dihydrogen Potassium Phosphate, Sodium Hydroxide, Polyethylene glycol 400, Triethyl citrate, Triethanolamine were bought from Loba chemie, Pvt. Ltd., Mumbai

Methods:

Ibuprofen microsponges were prepared by quassi emulsion solvent diffusion method by using different drug:

polymer ratio. In this method two major chemical phases were used for preparation of drug loaded Microspongic particles. First internal phase was prepared by dissolving Ibuprofen, Eudragit RS 100 and Triethylcitrate in dichloromethane. Triethylcitrate was used as plasticizer. In this procedure dichloromethane was an effective solvent for both drug and polymer. Second external aqueous phase consisting of 0.5%w/v polyvinyl alcohol was placed in magnetic stirrer. After preparation of both phases, internal phase was poured into external phase. The mixture was stirred at 500 rpm for 1 hour. Microsponges were formed by removal of dichloromethane from system. The formed microsponges were filtered, washed with distilled water and dried at room temperature**.** (3,4)

Table 1: Composition of various microsponge batches.

Components	F1	F2	F3	F4
Ibuprofen(mg)	50	150	250	350
Eudragit RS 100 (mg)	50	50	50	50
Triethylcitrate (%w/v)	1	1	1	1
Dichloromethane (ml)	5	5	5	5
Polyvinyl alcohol (%w/v)	0.5	0.5	0.5	0 .5

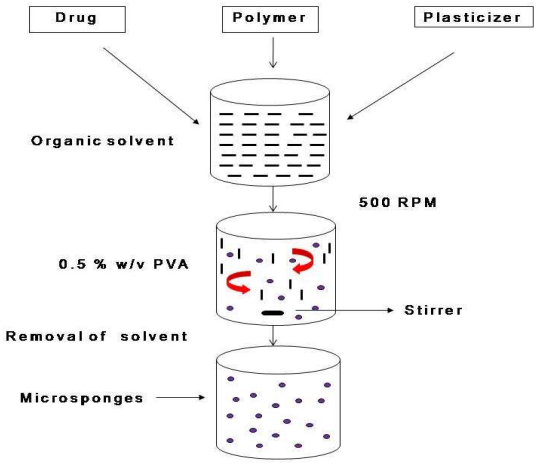

Figure 1: Formulation methodology of Ibuprofen microsponges

Evalua

Drug loading determination

An accurately weighed amount of Ibuprofen loaded microsponges (100mg) were dissolved in 100ml pH 7.4 phosphate buffer. The microsponges were soaked for 24 hours with stirring. The solution was filtered through Whatmann filter paper and analyzed by UV Spectrophotometer at 224 nm.(7)

Drug loading was calculated according to following equation-

$$\textbf{Drug loading} = \frac{Actual\ drug\ content\ microsponges}{Total\ amount\ of\ microsponges} \times \mathbf{100}$$

Table 2: Percent drug loading of batches from F1 to F4

Sr. No.	Batches	Drug Loading* (%w/w)
1	F1	9.88±0.22
2	F2	33.80±0.25
3	F3	52.84±0.31
4	F4	71.48±0.20

***Each value represents mean± standard deviation (n= 3)**

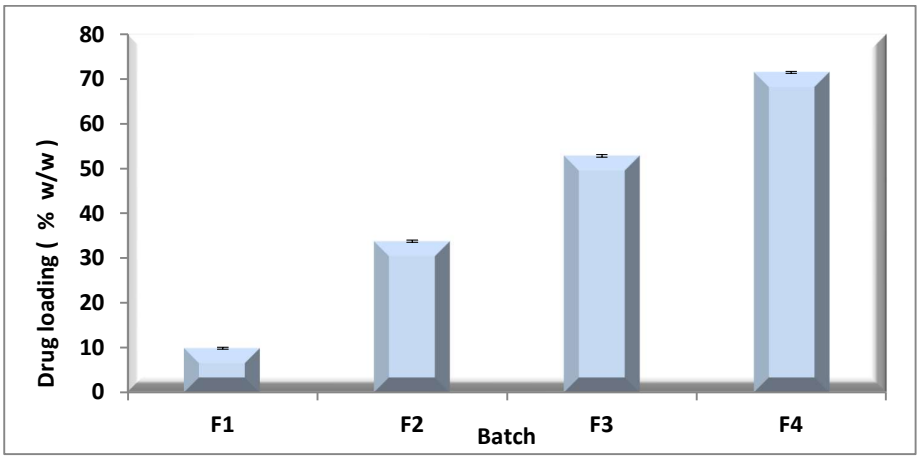

Figure 2: Percent drug loading of batches F1 to F4

Entrapment efficiency determination (5-6)

Actual drug content was determined spectrophotometrically and entrapment efficiency was determined by using the following formula-

$$\% \text{ EE} = \frac{Actual\ drug\ content\ in\ microsponges}{Theorotica\ \ drug\ content} \times 100$$

Table 3: Percent entrapment efficiency of batches from F1 to F4

Sr. No.	Batches	% Entrapment efficiency* (%w/w)
1	F1	19.76± 0.75
2	F_2	45.06±0.60
3	F_3	63.41±0.73
4	F4	81.71±0.88

***Each value represents mean± standard deviation (n = 3)**

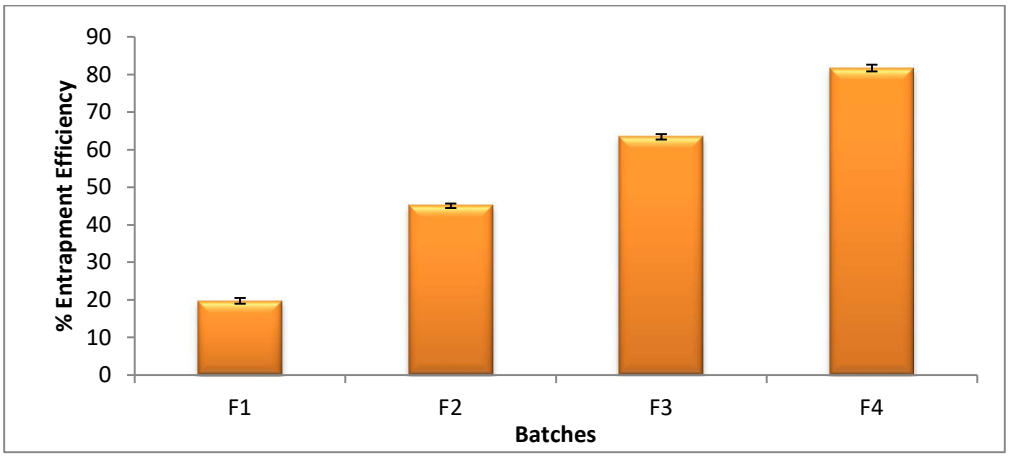

Figure 3: Percent entrapment efficiency of batches F1 to F4

Production yield (8)

Production yield of microsponges was determined by calculating accurately the initial weight of raw materials and last weight of microsponges obtained. It was determined by using following equation

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

Table 4: Percent production yield of batches F1to F4

Sr. No	Batches	Production yield(%w/w)*
1	F1	20.10± 0.11
2	F2	34.21±0.29
3	F3	45.46±0.32
4	F4	51.43± 0.25

***Each value represents mean ± standard deviation (n = 3)**

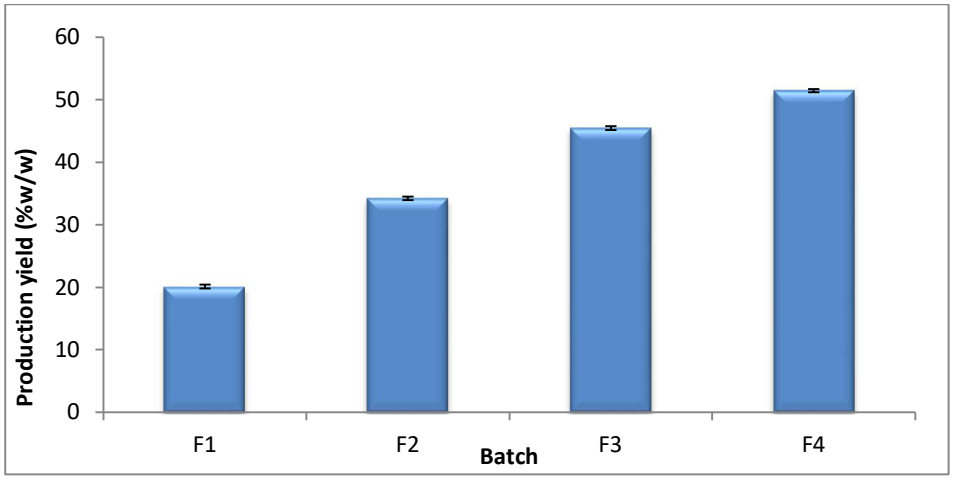

Figure 4: Percent production yield of batches F1 to F4

Determination of particle size (5)

The particle size of microspheres of different batches was measured by imaging system. Particle sizes of each batch were determined three times and mean values was taken.

Table 5: Particle size of batches from F1to F4

Sr. No.	Batches	Diameter(µm)*
1.	F1	51.10.±0.56
2.	F2	42.2±0.48
3.	F3	30.33±0.35
4.	F4	22.01±0.41

***Each value represents mean ± standard deviation (n = 3)**

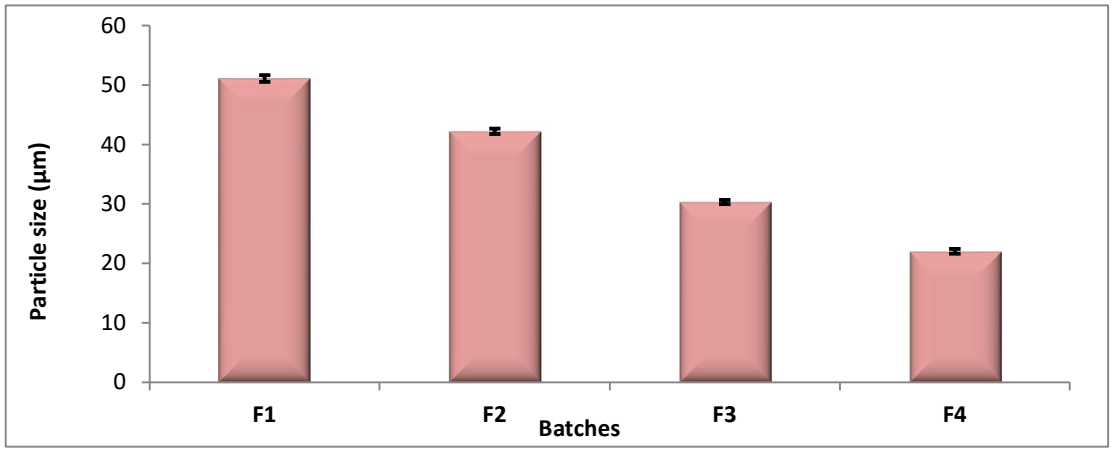

Figure 5: Particle size of batches F1to F4

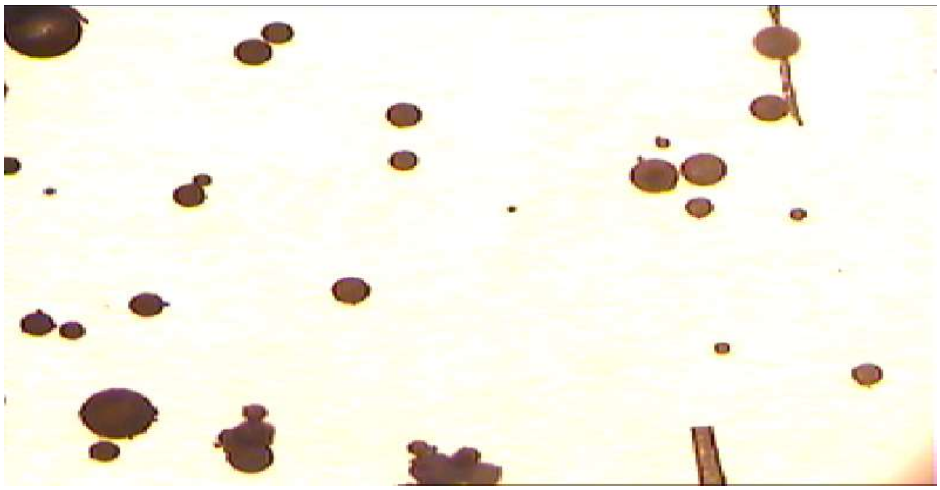

Figure 6: Photomicrograph of batch F3

***In vitro* drug release study (**7, 8)

In vitro release study of Ibuprofen microsponges was carried out using USP type 1 apparatus. Microsponges equivalent to 500 mg of Ibuprofen were weighed accurately and placed in muslin cloth .The dissolution medium used was 900ml of 7.4 phosphate buffer maintained at 32 ± 1^0 and stirred at 50 rpm. 5 ml of the dissolution medium was sampled at certain intervals; fresh dissolution medium was simultaneously replaced in the apparatus to keep the volume constant. The withdrawn samples were filtered and filtrate was assayed spectrophotometrically at 224 nm. Results of in vitro release are shown in **Table 6.**

Table 6: *In vitro* release of batches from F1 to F4

Time (Hours)	% Cumulative drug release*			
	F1	F2	F3	F4
0	0	0	0	0
1	23.40 ±0.04	24.30 ±0.04	37.80 ±0.08	38.71 ±0.25
2	26.23 ±0.01	35.55 ±0.05	44.31 ±0.05	46.31 ±0.10
3	33.9 ±0.04	41.05 ±0.10	51.75 ±0.06	58.95 ±0.05
4	40.28 ±0.04	49.36 ±0.10	55.93 ±0.44	61.10 ±0.06
5	44.98 ±0.03	60.41 ±0.07	64.40 ±0.16	73.17 ±0.09
6	46.81 ±0.04	66.12 ±0.06	77.02 ±0.12	84.31 ±0.15
7	48.14 ±0.03	72.77 ±0.03	81.94 ±0.53	97.80 ±0.03
8	53.71 ±0.02	79.45 ±0.05	84.19 ±0.05	-

***Each value represents mean ± standard deviation (n = 3)**

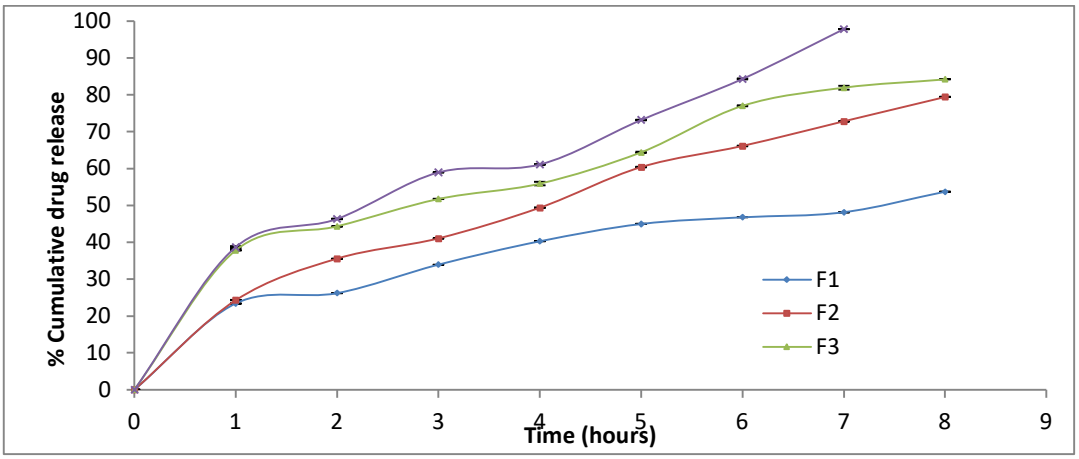

Figure 7: *In vitro* release of batches F1 to F4

Table 7: Release kinetic study of dissolution profiles of batches F1 to F4

Formulation	Parameters	Mathematical Models				
		Zero Order	First Order	Hixon - Crowell	Korsemeyer Peppas	Higuchi Plot
F1	R^2	0.93374	0.7152	0.8122	0.1323	0.9917
	Slope	5.6883	0.1414	0.6657	0.3897	0.0505
	Intercept	12.5188	0.8408	2.8864	0.3526	-0.220
F2	R^2	0.9776	0.7528	0.8734	0.4518	0.990
	Slope	9.061	0.1622	0.8693	0.4982	0.0408
	Intercept	11.420	0.8627	2.930	-0.3101	0.0008
F3	R^2	0.9409	0.6989	0.8160	0.7495	0.9905
	Slope	9.120	0.1573	0.8414	0.3427	0.0327
	Intercept	19.443	0.9659	3.622	-0.1347	-0.0524
F4	R^2	0.9311	0.7027	0.8204	0.8206	0.9894
	Slope	10.071	0.1587	0.8889	0.3505	0.0313
	Intercept	20.218	0.9799	3.702	-1174	-0.054

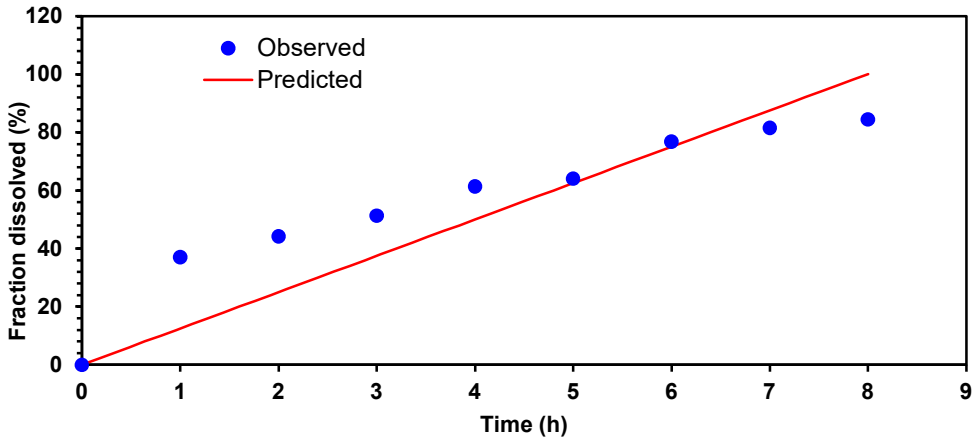

Figure 8: Zero order plot of batch F3

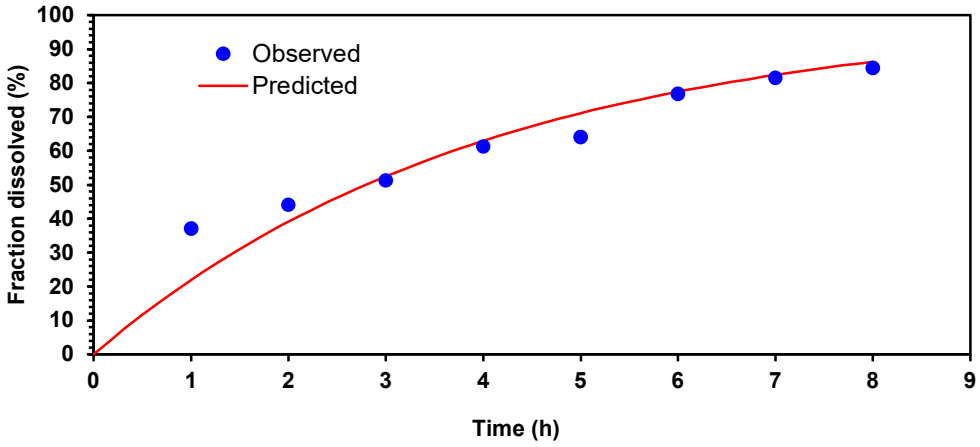

Figure 9: First order plot of batch F3

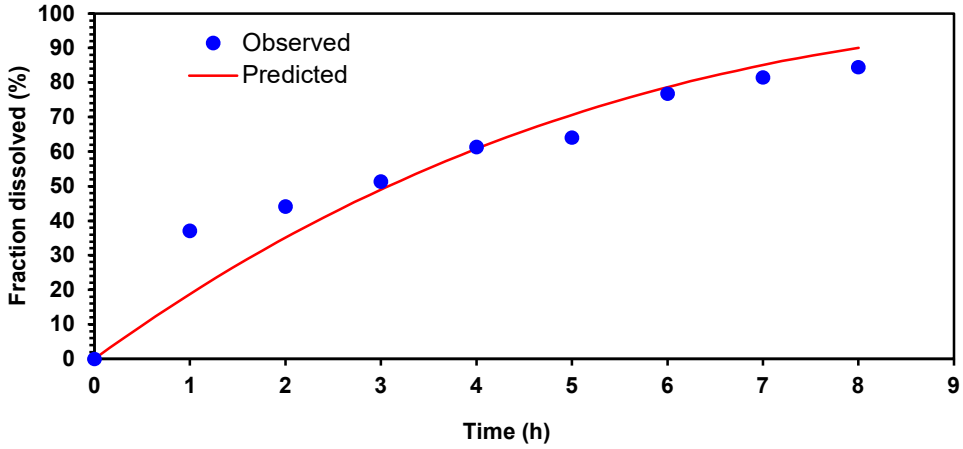

Figure 10: Hixon Crowell plot of batch F3

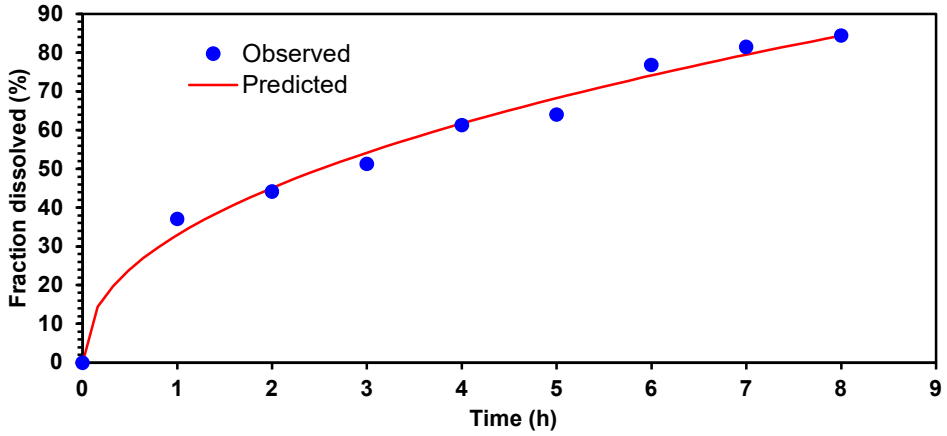

Figure 11: Korsemeyer peppas plot of batch F3

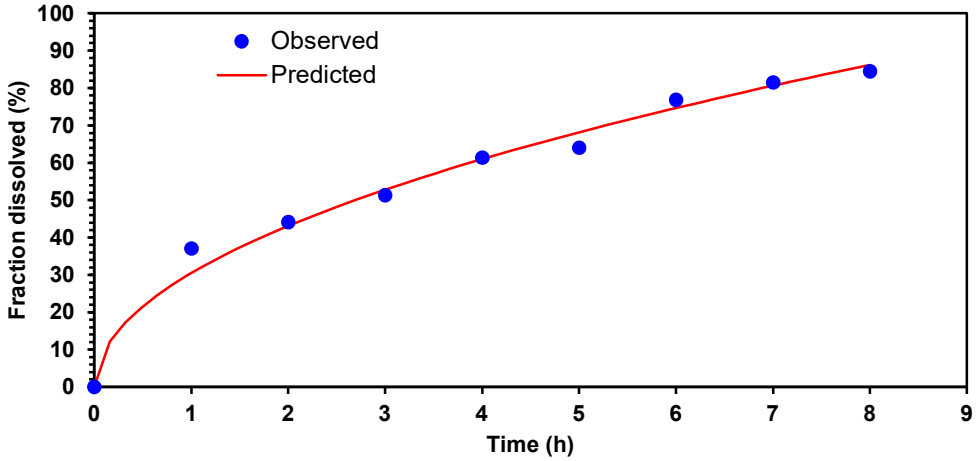

Figure 12: Higuchi plot of batch F3

Composition of Ibuprofen Microsponge Gel[39, 40, 41]

Accurately weighed quantity of Carbopol 940 was dissolved in water using stirrer. In another beaker , microsponges containing Ibuprofen (free or entrapped equivalent to 5%w/w) drug dissolved in methanol and added to Carbopol solution under continuous stirring , followed by addition of polyethylene glycol (PEG) 400.The Carbopol solution was neutralized by slowly adding triethanolamine with constant stirring until gel is formed. pH of final gel was determined.

Table 8: Composition of microsponge gel from G1 to G8

Sr. No	Ingredients	G1	G2	G3	G4	G5	G6	G7	G8
1	Ibuprofen(5 % w/w) (mg)	500	500	500	500	-	-	-	-
2	Optimized Microsponge (F3)(equivalent to 5%w/w of Ibuprofen)(in mg)	-	-	-	-	946	946	946	946
3	Carbopol 940 (%)	0.25	0.50	0.75	1.0	0.25	0.50	0.75	1.0
4	Methanol (ml)	2	2	2	2	2	2	2	2
5	Polyethylene glycol(ml)	1	1	1	1	1	1	1	1
6	Triethanolamine (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Distilled water upto(ml)	10	10	10	10	10	10	10	10

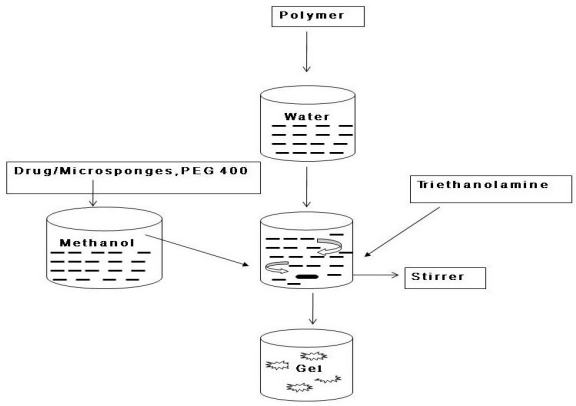

Figure 13 : Formulation of drug/ microsponge gel.

Drug content[33]

1.0 g of each gel formulations were taken in 100 ml volumetric flask containing 20 ml of phosphate buffer pH 7.4

and stirred for 30 min and allowed to stand for 24 hrs in case of microsponge loaded gel formulations. The volume was made upto 100 ml with phosphate buffer. Proper dilutions were made and the formulation was subjected to the spectrophotometric analysis. The content of drug was estimated spectrophotometrically by using standard curve plotted at λ_{max}224nm.

Table 9: Drug content of microsponge gel batches from G1 to G8

Sr. No	Batches	Drug content(%)*
1	G1	94.84 ± 0.12
2	G2	95.23 ±0.15
3	G3	96.76 ±0.13
4	G4	98.14 ±0.11
5	G5	90.55 ±0.10
6	G6	90.72 ± 0.17
7	G7	91.81 ± 0.13
8	G8	92.58 ± 0.14

***Each value represents mean ± standard deviation (n = 3).**

pH study[42]

pH of the various gel formulations were determined by using digital pH meter. The measurement of pH of each gel was done in triplicate and average values were calculated.

Table 10: pH of microsponge gel batches from G1 toG8

Sr. No	Batch	pH*
1	G1	6.76±0.15
2	G2	6.23±0.14
3	G3	6.40±0.26
4	G4	7.10±0.10
5	G5	7.26±0.20
6	G6	7.36±0.35
7	G7	7.42±0.32
8	G8	7.53±0.14

***Each value represents mean± standard deviation (n = 3)**

Viscosity study[43]

Viscosity of prepared gel was measured by Brookfield viscometer. The gels were rotated at the speed of 10 rotations per minute with spindle no.3

Table 11: viscosity of microsponge gel batches from G1 to G8 at37^0 C

Sr. No.	Batches	viscosity*(cp)
1	G1	5900±1.25
2	G2	6102±1.52
3	G3	7021±1.30
4	G4	7347±1.43
5	G5	7893±1.11
6	G6	7930±2.18
7	G7	8157±1.59
8	G8	8431±2.16

***Each value represents mean ± standard deviation(n = 3)**

Spreadability[44]

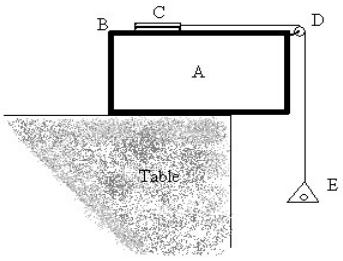

Figure 14: Spreadability test apparatus

A= Wooden box, B= Lower glass Slide, C= Upper Glass Slide, D= Pulley, E= Weighing pan

Spreadability of formulations was determined by an apparatus suggested by Multimer et al. which was fabricated in laboratory and used for study. The apparatus consist of a wooden block with a fixed glass slide and movable glass slide with one end tied to weight pan rolled on the pulley, which was in horizontal level with fixed slide.

Table 12: Spreadability of microsponge gel batches from G1 to G8

Sr. No.	Batches	Spreadability (g.cm/sec)
1.	G1	12.36±0.01
2.	G2	12.29±0.06
3.	G3	11.53±0.03
4.	G4	11.37±0.05
5.	G5	12.65±0.03
6.	G6	11.71±0.04
7.	G7	11.43±0.01
8.	G8	11.29±0.05

***Each value represents mean ± standard deviation (n = 3)**

Rheological behavior[49]

The rheologies of prepared formulations were studied using Brookfield viscometer (CAP-2000). The sample was placed on temperature sensitive plate. Temperature was kept at 37 ± 1^0 C. Cone no. 3 was held on the plate and speed of 10,20, 30, 40,50,60,70,80 rpm were selected. Different viscosities at respective spindle speeds were obtained for an ascending and descending curve. Shearing stress was calculated by using following formula.

$$Shear\ stress = viscosity \times shear\ rate$$

Rheograms were obtained by plotting rate of shear on y-axis versus calculated value of shear stress on x-axis. Rheogram of all formulations were shown respectively in **Figure 43 to 50.**

Table 13: Rheological studies of microsponge gel batches G1 to G4

Sr. No		RPM	G1		G2		G3		G4	
			Shear rate (sec^{-1})	Shear stress (dyne/cm^2)	Shear rate (sec^{-1})	Shear stress (dyne/cm^2)	Shear rate (sec^{-1})	Shear stress (dyne/cm^2)	Shear rate (sec^{-1})	Shear stress (dyne/cm^2)
1	Ascending	10	133	1084700	133	1211566	133	1177151	133	1049769
2		20	267	1238454	267	1473698	267	1926405	267	1447407
3		30	400	1413600	400	1752400	400	28260000	400	1710400
4		40	533	1612858	533	2039416	533	3527269	533	1934619
5		50	667	1987542	667	2444905	667	4077621	667	2184875
6		60	800	2154782	800	2734400	800	4396000	800	2516000
8		70	933	2354872	933	3071010	933	4628613	933	2809946
9		80	1067	2483380	1067	3202538	1067	4534150	1067	3278247
10	Descending	70	933	2465287	933	3178000	933	4223200	933	3069658
11		60	800	2315200	800	2988800	800	3920800	800	2710400
12		50	667	2154114	667	2705352	667	3524845	667	2438752
13		40	533	1890079	533	2294769	533	2876068	533	2203093
14		30	400	1663200	400	2005600	400	2265200	400	1961600
15		20	267	1452879	267	1806556	267	1670352	267	1692672
16		10	133	1239688	133	1563287	133	887908	133	1477768

Table 14: Rheological study of microsponge gel batches G5 to G8

Sr. No		RPM	G5		G6		G7		G8	
			Shear rate (sec^{-1})	Shear stress(dyne/cm)	Shear rate(sec^{-1})	Shear stress(dyne/cm)	Shear rate(sec^{-1})	Shear stress(dyne/cm)	Shear rate (sec^{-1})	Shear stress(dyne/cm^2)
1	Asce	10	133	933793	133	1054690	133	1163542	133	1249769
2		20	267	182765	267	1828950	267	1836852	267	1447407
3		30	400	261960	400	2769200	400	2687541	400	1810400
4		40	533	317829	533	3797625	533	3652421	533	2234619

5		50	667	369711	667	4458995	667	4352872	667	2584875
6		60	800	418000	800	4940800	800	4635891	800	2816000
8	Ending	70	933	430399	933	5235658	933	5125525	933	3009946
9		80	1067	465745	1067	5661925	1067	5536421	1067	3478247
7		70	933	401520	933	5495370	933	5364821	933	3269658
8		60	800	355680	800	5220000	800	5124872	800	3110400
9		50	667	288455	667	4907820	667	4789525	667	2838752
10		40	533	224305	533	4393440	533	4236998	533	2603093
11		30	400	156240	400	3280000	400	3422151	400	2261600
12		20	267	107891	267	2318094	267	2269752	267	1892672
13	Descending	10	133	694728	133	1689153	133	1456824	133	1677768

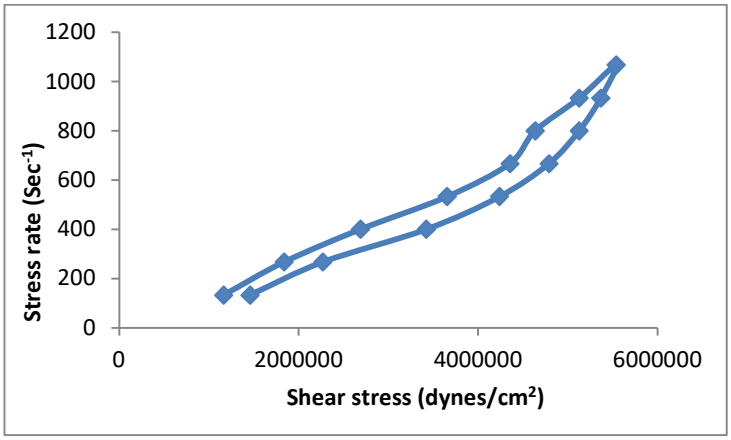

Figure 15: Rheological study of batch G7

***In vitro* diffusion studies**[50]

The release of Ibuprofen from optimized microsponge gel was determined by membrane diffusion technique using Franz diffusion cell. The microsponge gel equivalent to 5%w/w of Ibuprofen was taken in donor compartment. The donor and receptor compartment were separated by synthetic cellophane membrane. The synthetic cellophane membrane was mounted between donor and receptor compartment of cell. The receptor medium was filled with phosphate buffer pH 7.4. The assembly was stirred at 200 rpm and receptor compartment was replenished with equal volume of phosphate buffer. Aliquots each of 1 ml was withdrawn periodically at an interval of 1, 2, 3, 4, 5, 6, 7 and 8 hrs and replaced by an equal volume of receptor medium. The aliquots were suitably diluted with receptor medium and analyzed by UV visible spectrophotometer.

Table 15: *In vitro* release of batches G1 to G4

Time (Hours)	% cumulative drug release			
	G1	G2	G3	G4
0	0	0	0	0
1	29.42±0.06	29.32±0.17	27.79±0.08	27.72±0.15
2	36.05±1.04	35.33±0.43	34.79±0.31	34.73±0.06
3	44.82±0.05	41.83±0.10	41.38±0.22	41.28±0.05
4	51.60±0.69	52.33±0.61	48.17±0.03	47.87±0.15
5	60.99±0.11	61.38±0.27	56.81±0.36	56.69±0.19
6	69.96±0.07	68.92±0.65	69.33±0.26	64.19±0.15

7	82.36±0.24	78.78±0.36	73.22±0.92	72.55±0.20
8	91.04±0.30	88.78±1.27	83.92±0.52	81.72±0.26

***Each value represents mean ± standard deviation(n = 3)**

Table 16: *In vitro* release of batchesG5 to G8

Time (Hours)	% Cumulative drug release*			
	G5	G6	G7	G8
0	0	0	0	0
1	25.26±0.02	22.35±0.040	19.19±0.06	18.35±0.17
2	32.43±0.04	29.12±0.08	26.31±0.08	24.26±0.03
3	40.32±0.05	36.25±0.01	34.54±0.03	32.08±0.06
4	48.19±0.08	43.28±0.02	40.40±0.02	38.34±0.10
5	56.21±0.03	51.23±0.03	49.28±0.02	45.43±0.29
6	64.17±0.06	58.08±0.02	56.01±0.03	53.02±0.03
7	72.28±0.10	67.15±0.08	64.36±0.03	61.75±0.03
8	80.41±0.04	76.28±0.02	74.11±0.02	70.54±0.02

Table 17: Release kinetic study of *In vitro* diffusion of batches G1 to G8

Formulation	Parameters	Mathematical Models				
		Zero order	First Order	Hixon–Crowell	Korsemeyer Peppas	Higuchi Plot
G1	R^2	0.9818	0.7510	0.880	0.4857	0.9966
	Slope	10.116	0.164	0.9159	0.4057	0.0390
	Intercept	11.339	0.884	3.013	-0.2415	-0.034
G2	R^2	0.9820	0.7502	0.8781	0.444	0.993
	Slope	9.987	0.1637	0.9025	0.3984	0.0394
	Intercept	11.040	0.8810	3.000	-0.2475	-0.022
G3	R^2	0.9786	0.7489	0.8741	0.3860	0.9961
	Slope	9.274	0.1615	0.8743	0.3908	0.0418
	Intercept	11.280	0.8724	2.960	-0.2626	-0.043
G4	R^2	0.9769	0.7442	0.8681	0.3793	0.9960
	Slope	8.928	0.1595	0.854	0.3888	0.0420
	Intercept	11.70	0.8743	2.982	-0.2633	0.0447
G5	R^2	0.9833	0.7613	0.8846	0.3613	0.988
	Slope	9.167	0.1632	0.8768	0.4568	0.0414
	Intercept	9.796	0.8472	2.810	-0.311	0.0287
G6	R^2	0.9806	0.7559	0.8762	0.2560	0.996
	Slope	8.325	0.1588	0.8298	0.4084	0.0463

	Intercept	9.947	0.8395	2.874	-0.318	-0.030
G7	**R^2**	0.9857	0.770	0.8897	0.2222	0.9980
	Slope	8.399	0.1612	0.8414	0.4440	0.0488
	Intercept	8.341	0.8143	2.6321	-0.3587	-0.0180
G8	**R^2**	0.9878	0.7806	0.8975	0.1463	0.9978
	Slope	8.085	0.1612	0.8295	0.4417	0.052
	Intercept	7.022	0.7877	2.845	-0.3939	-0.016

Stability study[49, 51]

The optimized formulation of Ibuprofen loaded microsponge gel was packed in aluminum collapsible tubes and subjected to stability studies at 40^0C± 2^0C/75% ± 5% RH for a period of 3 months. Formulations were evaluated at periodic intervals for pH, viscosity, and drug content and drug release profiles.

Table 18: Evaluation of optimized batch G7at different time intervals after storage under 40 ± 2^0C/ 75 ± 5% RH

Temperature/parameters Evaluated		**0 month**	**1month**	**2 months**	**3months**
40^0C±2^0C/ 75% ± 5% RH	pH	7.42± 0.32	7.45± 0.34	7.43± 0.31	7.36 ±0.25
	Viscosity* (centipoise)	8157±1.59	8152±1.56	8149±1.51	8146 ±1.50
	Spreadability*	11.43±0.11	11.41±0.01	11.36±0.10	11.32±0.20

	Drug content (%)*	91.81±0.30	91.79±0.15	90.64±0.01	90.62±0.11
	Cumulative% drug release*	74.11±0.20	74.32± 0.03	74.18 ±0.04	74.04±0.07

Table 19: *In vitro* release profile of batch G7 kept for stability study

Sr. No	Time(Hrs)	% Cumulative drug release*			
		0 month	1 month	2 months	3 months
1	0	0	0	0	0
2	1	19.19 ± 0.06	18.96 ± 0.02	18.41 ± 0.03	18.10 ± 0.04
3	2	26.31±0.08	26.25 ± 0.07	26.10 ± 0.08	25.89 ± 0.05
4	3	34.54±0.03	34.33 ±0.05	33.98 ±0.05	33.72 ± 0.06
5	4	40.46±0.02	40.22 ± 0.02	39.84 ± 0.03	39.64 ± 0.03
6	5	49.28±0.02	48.75 ± 0.01	48.61 ± 0.07	48.55 ± 0.02
7	6	56.01±0.09	55.98 ± 0.08	55.57 ± 0.06	55.33 ± 0.04
8	7	64.36±0.03	64.14 ± 0.02	63.82 ± 0.02	63.40 ±0.03
9	8	74.11±0.02	74.32 ± 0.03	74.18 ± 0.04	74.04± 0.07

Discussion

Ibuprofen is non-steroidal anti-inflammatory drug. The drug has a half-life of 1 to 2 hours. Because of its short biological half-life the drug has to be administered frequently. Furthermore oral Ibuprofen causes irritation in gastric mucosal membrane and possess a bitter taste and after taste. Therefore present work aims at designing novel microsponges as carriers for topical delivery of Ibuprofen which minimizes its gastro intestinal side effects and provides consistent drug levels at application site for longer period of time.

The compatibility parameters were studied using IR method. Solution of Ibuprofen was scanned for its maximum absorbance, maximum absorbance was found on 224 nm. Standard calibration curve was prepared using phosphate buffer pH 7.4. Microsponges were developed using novel quassi emulsion solvent diffusion method. The formulations were prepared using different drug: polymer ratios. The microsponges were characterized for loading efficiency, entrapment efficiency, particle size and *in vitro* drug release. The batch F3 showed optimum loading efficiency, entrapment efficiency and maximum drug release upto 8 hours, associated with burst effect. The drug release profile was fitted to Higuchi's model and showed Fickian drug release mechanism

Microsponges were incorporated into gel prepared with different polymer concentrations. The gel formulations were evaluated for % drug content, pH, viscosity, spreadability and *in vitro* diffusion study. Rheological properties of all formulations were studied and from rheogram it was proved that all gel formulations exhibited shear thinning system with thixotropic nature. From all formulations, formulation G7 was found to be promising. The optimized formulation G7 showed optimum pH, viscosity, spreadability and 73.45 ± 0.02% drug release at the end of 8 hour. The stability studies were carried out on optimized batch G7 at 40 ± 2 ^{0}C and 75 ± 5 % RH for 3 months. The gel was evaluated for percent cumulative drug release after 0, 30, 60 and 90 days. No significant changes in drug release were obtained hence it was concluded that the optimized batch was stable.

Conclusion

A controlled release topical drug delivery of Ibuprofen developed as a microsponge loaded gel offers solubilizing matrix for the drug, served as a local depot for controlled drug release and provided a rate limiting matrix barrier

for modulation of drug release.

Conflict of interest:

Author declares no conflict of interest.

Source of funding

None

Data availability

The data used to support the findings of this study are available from the corresponding or first author upon request

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