"Design and Evaluation of CelecoxibMicrosponge"

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ABSTRACT

Purpose: Celecoxibmicrosponges systems were developed to control the drug release for topical application.
Methods: Celecoxibmicrosponges were prepared using Eudragit RS100 and ethyl cellulose by quasi emulsion solvent diffusion method. Prepared microsponge systems were evaluated for production yield, loading efficiency,drug content, drug interaction studiesand *in vitro* drug release studies. Optimized microsponges were incorporated into carbopol gels and evaluated for *in vitro* drug release and skin irritation tests.
Results: The FTIR results suggest no interaction between the drug and excipients. The drug content was uniform and no significant difference was observed for production yield and loading efficiency amongst all the formulations. The release was found to be steady after 2 h and was extended up to 8 h with sustained action and as the concentration of the polymer increases the drug release was decreases. Neither edema nor symptoms of adverse affects were observed in skin irritation studies.
Conclusion: Celecoxibmicrosponges were conveniently prepared with method adapted and the results were found to be reproducible.
Keywords: Microsponge, Eudragit, Ethyl cellulose, Carbopol, *In vitro* studies.

INTRODUCTION

To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system.Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery systemusing the skin as portal of entry [1,2]. Transdermal delivery systemhas improved the efficacy and safety of many drugs that may be better administered through skin, but TDS is not practical for delivery of materials whose final target is skin itself. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis.Application of topical drugs suffers many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc that often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body. The microsponge delivery system fulfills these requirements.

Microsponge delivery system is "patented,-linked, porous, polymeric microsphere polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response totrigger"[3]. It is a unique technology for the controlled release of topical agents and recently for oral administration.These systemsconsists of microporous beads, typically 10-25 microns in diameter, loaded with active agent, when applied to the skin, releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc) and are employed for the improvement of performance of topically applied drugs [5-7].Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release and that can bind, suspend or entrap a wide variety of substances and can be incorporated into a formulated product, such as a gel, cream, liquid or powder[8-10].

Celecoxib isa nonsteroidalantiinflammatory drugable to selectively inhibit COX-2 activity and exhibits antiinflammatory, analgesic and antipyretic activities.

It has been used in the treatment of rheumatoid arthritis, osteoarthritis, acute pain. In the present investigation an attempt is made to design and evaluate celecoxibmicrosponge systems with novel polymers and studied their*in vitro* release properties.Optimized microsponges were incorporated into carbopol gels and evaluated for *in vitro* drug release and skin irritation tests.

MATERIALS AND METHODS

Celecoxib obtained from Shasun pharmaceutical Ltd Hp. Poly vinyl alcohol, Ethyl cellulose, Eudragit RS 100, Ethanol, Methanol and Triethyl citrate are obtained from SD fine chemical Ltd. Triethanolamine was obtained from Qualigens fine chemicals, and Carbopol 934 was obtained from Yarrow chem. Products.

Preparation of celecoxibmicrosponge

Celecoxibmicrospongesystems were prepared by quasi emulsion solvent diffusion method[13-15] using eudragit RS100, ethyl cellulose alone and in combination at different drug: polymer ratios viz., 2:1, 1:1, 1:2. The external phase containing 500 ml of 0.5% w/v poly vinyl alcohol in water was placed in the vessel fixed with propeller stirrer rotating at 600 rpm, to this add slowly internal phase consist of accurately weighed quantities of celecoxib and eudragit RS100, ethyl cellulose alone and in combination dissolved in 10 ml of ethanol and add 1ml of triethyl citrate as plasticizer. The system was thermally controlled at 25^0C in a water bath, initial 30 min rotation permit the formation of microsponges and continue stirring for about 2hr to get desired rigid microsponges. The rigid microspongeswere filtered through the whatmann filter paper, washed repeatedly with distilled water and dried at room temperature. The dried microsponges were kept in a dried vial for further study. The formulae of various microsponge systems are shown in table 1.

Preparation of optimized microsponge incorporated carpopolgels[16-19]

Dissolve accurately weighed quantity of carbopol 934 in 10ml distilled water to this add PEG 400 which is previously contained 100mg of optimized microsponge formulations viz., F-3, F-6 and F-9 with constant stirring. To the whole mixture add drop wise triethanolamine until transparent gel was obtained. Stirring was stopped to escape entrapped air, further formed gel was stored in an air tight container for further study. The formulae of various microsponge incorporated carbopol gel were given in table 2.

Evaluation of microsponges

Production yield[20]

Thedried microsponges of each batch are weighed separately and percentage yield is calculated by using following equation.

$$\text{Percentage yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100$$

Loading efficiency[20]

100 mg of microsponges were accurately weighed. They were powdered and extracted with 100 ml of methanol. Further it was serially diluted with 2% w/v sodium lauryl sulphatesolution. The resulting solution was analysed for celecoxib content by measuring absorbance in a UV-spectrophotometer at 255nm. The studies were carried out in triplicate. Loading efficiency (%) was calculated using the formula.

$$\text{Loading efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Drug content

100 mg of microsponges were weighed, powdered and extracted with 100ml of methanol followed by filtration. The filtrates was diluted with 2% w/v sodium lauryl sulphate solution and measure the absorbance at 255nm. The drug content was analyzed from the calibration curve. The studies were carried out in triplicate.

FTIR spectral studies

The compatibility between drug and polymers were detected by FTIR studies. The FTIR spectra of drug and microsponge formulations were obtained on Perkin Elmer 1600 series, (USA). The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

***In vitro*dissolution studies[14]**

The release of celecoxib from microsponge was investigated in 2% w/v sodium lauryl sulphate solution as a dissolution medium (900 ml) using USP type I apparatus. A sample of microsponge equivalent to 50 mg of celecoxib was taken in the basket. A speed of 60 rpm and temperature of 37 ± 0.5^0c was maintained throughout the experiment. At fixed time intervals, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using Hitachi U-2000 spectrophotometer at 255nm.The studies were carried out in triplicate. The *in vitro* dissolution data were calculated by using dissolution software viz., PCP DISSO V3.0. and are given in table 4.

Evaluation ofmicrosponge gels

Drug content

Microsponge gel equivalent to 25mg of celecoxibwas extracted with 100ml of methanol followed by filtration. The filtrate was diluted with 2% w/v sodium lauryl sulphate solution and measures the absorbance at 255nm. The drug content was analyzed from the calibration curve. The studies were carried out in triplicate.

SEM: For morphology and surface topography, prepared microsponges can be coated with gold palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy[21].

***In vitro* diffusion studies[20]**

The release of celecoxib from optimized microsponge gels were determined using membrane diffusion technique. The microsponge gels equivalent to 50 mg of celecoxib was used for the diffusion study. The gel was taken in a glass tube having a diameter 2.5 cm with an effective length of 8 cm that was previously covered with soaked osmosis cellulose membrane, which acts as a donor compartment. The glass tube was placed in a beaker containing 250 ml of 2% w/v sodium lauryl sulphate solution, which acts as receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing gel was just touched (1-2mm deep) the surface of diffusion medium. The temperature of receptor medium maintained at 37 ± 10^0C and the medium was agitated at 100 rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analysed at 254 nm using 2% w/v sodium lauryl sulphate solution as blank. The *in vitro* drug diffusion data was given in table 4 and computed by dissolution softwarePCP-DISSO V.3.

Skin irritation study[21-23]

Albino Rabbits (2-2.5kg) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of rabbits and area of $4cm^2$ was marked on both the sides. One side served as control white the other side was test. Prepared optimized microsponge gel was applied (500 mg/rabbits) twice a day for 7 days and the site was observed for any sensitivity and reaction if any, was graded as 0, 1, 2, 3 for no reaction, slightly patchy erythema, slightly but conflict or moderate patchy erythema, severe erythema with or without edema respectively.

RESULTS AND DISCUSSION

Discussion

The production yield was found to be in the range of 85.21% to 95.09% and loading efficiency was found to bein the range of 75.80±0.41 to 88.50±0.38 for F-1 to F-9 formulations. Theproduction yield and loading efficiency data was subjected for statistical analysis shows no significant difference was observed amongst the formulations ($p < 0.05$).The drug content was found to be in the range of 97.50±0.32 to 99.12±0.28 for F-1 to F-9 formulations. The low standard deviation (SD) and low coefficient of variation (CV) i.e.,< 2 indicating drug distribution was uniform in all the microsponge formulations.

The FTIR spectra of pure celecoxib shows characteristic bands -NH symmetric stretching at 3226.03 cm^{-1}, S=O symmetric stretching at 1345.50 cm^{-1}, S-O asymmetric stretching at1132.30 cm^{-1} and $-CF_3$ bending at 1276.30 cm^{-1} and 1225.98 cm^{-1}. The characteristic celecoxib bands viz., -NH symmetric stretching was observed in the range of 3212.97 cm^{-1} to 3217. 59 cm^{-1} ; S=O symmetric stretching 1345.20cm^{-1} to 1347.45cm^{-1}; S-O asymmetric stretching celecoxib 1163.14cm^{-1} to 1164.99cm^{-1} and $-CF_3$ bending 1272.14cm^{-1} to 1274.29cm^{-1} and 1233.48cm^{-1} to 1236.17cm^{-1} in all microsponge systems. The FTIR spectra were given in figure 1 and table 3. All the characteristic celecoxib bands were observed in microsponge systems with slight shifting towards higher/lower wave length due to mild to no interaction suggest lack of significant interaction between celecoxib and selected polymers used in the formulation of microsponge systems. The FTIR spectrum of microsponge formulations shows all other peaks observed with individual compound have remain unaffected indicates microsponges formed were not a chemical reaction product, hence, the drug exists in original form and available for the biological action.

The *in vitro* drug dissolution was studied by using standard procedure and conditions. The *in vitro* data, kinetic regression model fitting values and *in vitro* profiles were given in tables 4 and figures 4-6. The cumulative percent drug release was about 47.34, 45.54 and 43.57 for F-1, F-2 and F-3; 47.94, 44.91 and 42.56 for F-4, F-5 and F-6; 49.34, 46.10 and 44.57 for F-7, F-8 and F-9 formulations at the end of 1 hr. The release was found to be steady after 2 hr and was extended up to 8 hr with sustained action and as the concentration of the polymer increases the drug release was decreases. To ascertain the drug release mechanism and release rate, data of the above formulations were model fitted by using PCP disso V3.0 dissolution software. In all the microsponge systems the best fit model was found to be KorsemayerPeppas with exponential `n' value was found to be 0.3461, 0.3492, 0.3710for F-1, F-2, F-3;0.3624, 0.3818, 0.4044 for F-4, F-5, F-6; 0.3456, 0.3465, 0.3585 for F-7, F-8, F-9; In all the microsponge systems 'n' value < 0.5 suggesting that the drug was released

fickian release mechanism was diffusion controlled i.e., the drug was released by erosion followed by diffusion controlled.

F-3, F-6 and F-9 microspongesystems were selected as optimized batches and were converted into carbopol 934gel formulations and are evaluated for drug content, primary skin irritation test and diffusion studies. The drug release profiles were given in table 4 and figure 7. The drug content was found to be 97.00 ± 0.17, 98.50 ± 0.25 and 98.35± 0.15 for VF-1, VF-2 and VF-3 gel formulations. The cumulative percent drug from the gels was 85.37±0.26, 84.51±0.37 and 88.53±0.35 for VF-1, VF-2 and VF-3 gel formulations respectively. The best fit model was found to be matrix with exponential `n' value was 0.6954, 0.5862 and 0.5259. In all the microsponge converted gels the peppas exponential 'n' value > 0.5 suggesting that the drug was released by non fickian mechanism i.e., the drug was released by erosion followed by diffusion controlled.

The skin irritation test was performed on rabbits according to Draize patch test. During the study any kind of adverse effects like swelling, edema and redness were not observed after the application of gel at the end of 2, 3, 5 and even after 7 days. The results suggest that neither there is edema nor symptoms of adverse effects hence `0' score was given after each observation indicating celecoxibmicrosponge can be conveniently incorporated into gels without any irritation. The selected microsponge incorporated carbopol gel formulation showed an irritation potential of 1.4976 shown in table5. Thus proving to be non-irritant as it was mentioned by Van- Abbé et al[24]., that a value between 0 and 9 in an irritancy test indicates that the applied formulation is generally non-irritant to human skin (Van-Abbé et al., 1975).

CONCLUSIONS

Celecoxibmicrosponges were conveniently prepared by quasi emulsion solvent diffusion method using eudragit RS 100 and ethyl cellulose as rate controlling polymers. The release was found to be steady after 2 hr and was extended up to 8 hr with sustained action. The best fit model was found to be peppas and the drug was released fickian release mechanism was diffusion controlled. The optimized microsponge gels were prepared in carbopol and the skin irritation test was performed on rabbits according to Draize patch test. The results suggest that neither there is edema nor symptoms of adverse effects.

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Figure Legends.

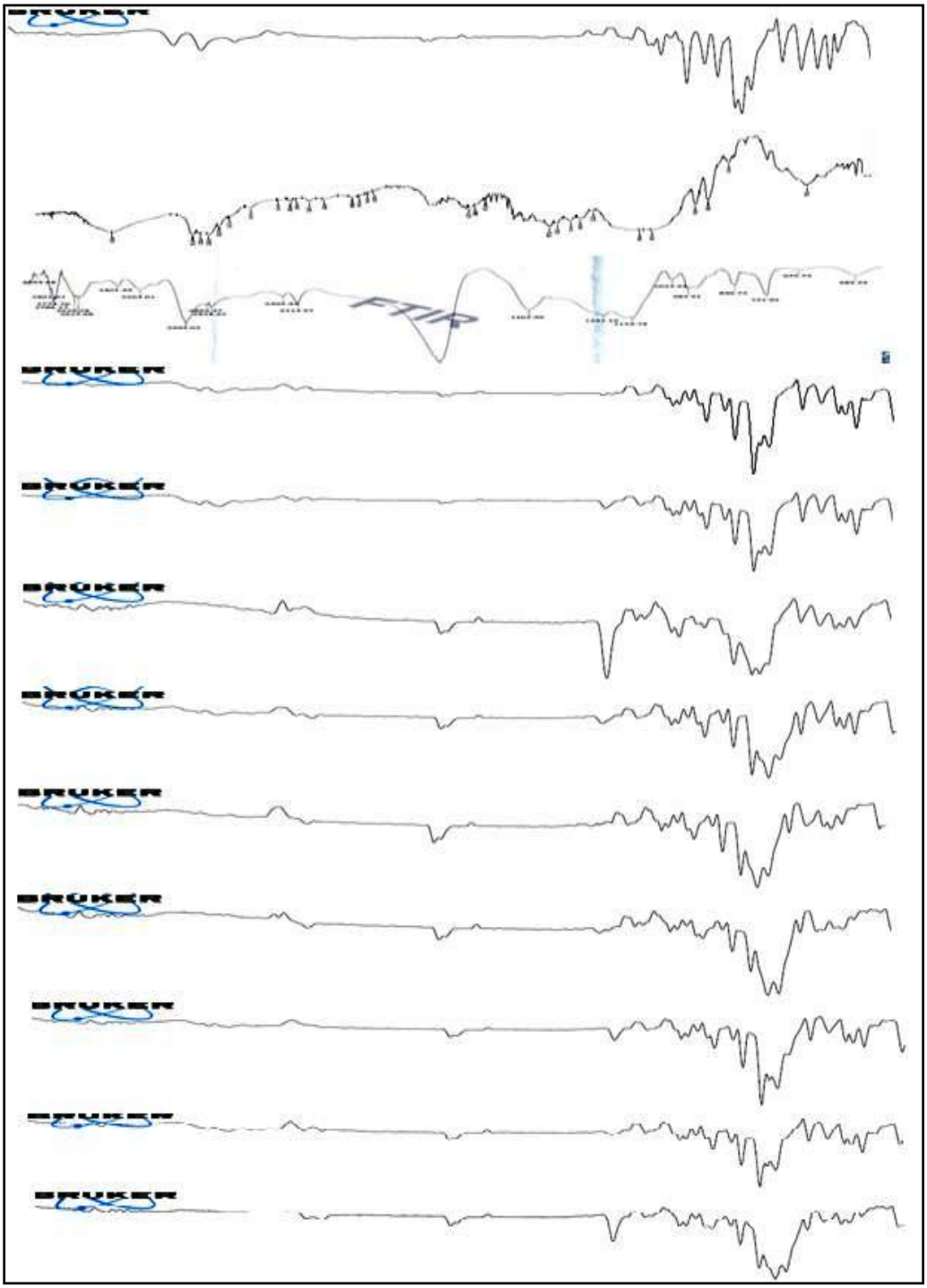

Fig.1. FTIR spectra of celecoxib, ethyl cellulose, eudragit RS 100 and F-1 to F-9microsponge formulations.

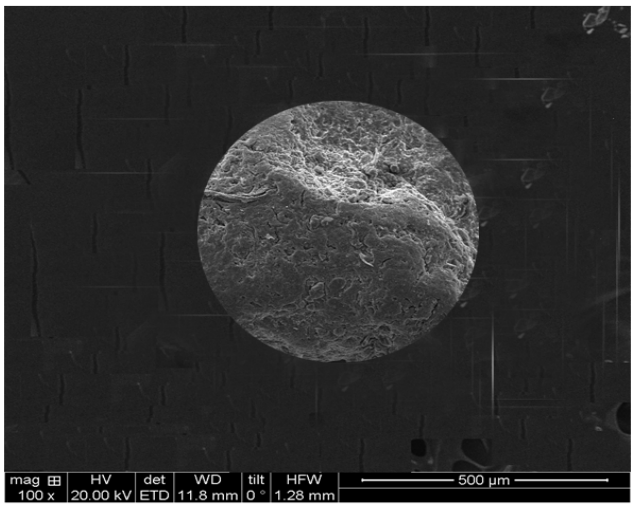

Fig.2. SEM photograph of F-3 microsponge formulation.

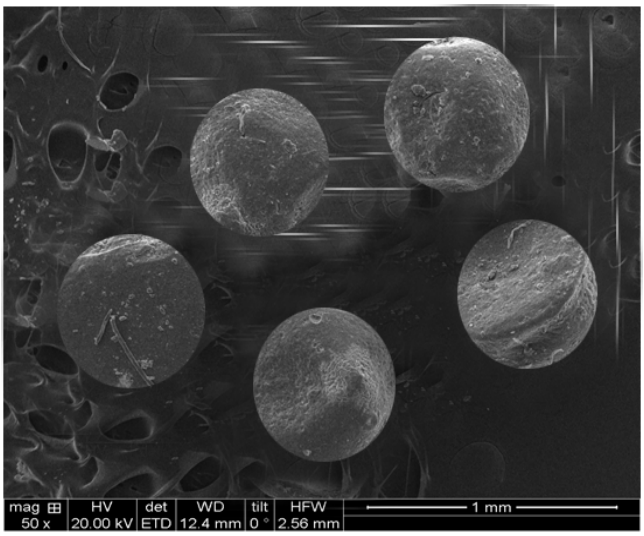

Fig.3. SEM photograph of F-6 microsponge formulation.

Table 1: Different formulae of microsponge.

BATCHES	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Drug: polymer Ratio	2:01	1:01	1:02	2:01	1:01	1:02	2:1(1:1)	1:1(1:1)	1:2(1:1)
					Internal phase				
Celecoxib (mg)	1000	500	500	1000	500	500	1000	500	500
Eudragit RS 100 (mg)	500	500	1000	-	-	-	250	250	500
Ethyl cellulose (mg)	-	-	-	500	500	1000	250	250	500
Ethanol (ml)	10	10	10	10	10	10	10	10	10
Triethyl citrate (ml)	1	1	1	1	1	1	1	1	1
					External phase				
PVA (G)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Water (ml)	500	500	500	500	500	500	500	500	500

Table 2: Different formulae of microsponge incorporated gel.

Ingredients	Plane gel	VF-1-Gel	VF-2-Gel	VF-3-Gel
Optimized microsponge(equivalent to 100mg of celecoxib)	-	300mg	300mg	300mg
Carbopol 934	100mg	100mg	100mg	100mg
Distilled water	10ml	10ml	10ml	10ml
Tri ethanol amine	2-3 (drops)	2-3 (drops)	2-3 (drops)	2-3 (drops)

Table 3: FTIR interpretation data of microsponge formulations.

		FTIR DATA		
Batches	**NH Symmetric Stretching**	**S-O Asymmetric Stretching**	**S=O Symmetric Stretching**	**CF3**
Celecoxib	3226.03 cm^{-1}	1132.30 cm^{-1}	1345.50 cm^{-1}	1276.30 cm^{-1}
				1225.98 cm^{-1}
F-1	3215.52 cm^{-1}	1164.70 cm^{-1}	1345.92 cm^{-1}	1274.17 cm^{-1}
				1235.97 cm^{-1}
F-2	3214.56 cm^{-1}	1164.03 cm^{-1}	1345.77 cm^{-1}	1274.29 cm^{-1}
				1236.17 cm^{-1}
F-3	-	1163.95 cm^{-1}	1346.12 cm^{-1}	1233.48cm^{-1}
F-4	3217.59 cm^{-1}	1163.14cm^{-1}	1345.20 cm^{-1}	1273.75 cm^{-1}
				1234.41 cm^{-1}
F-5	-	1163.81 cm^{-1}	1346.09 cm^{-1}	1273.89 cm^{-1}
				1234.92 cm^{-1}
F-6	-	1164.07 cm^{-1}	1347.45 cm^{-1}	1234.71 cm^{-1}
F-7	3213.22 cm^{-1}	1164.99 cm^{-1}	1345.81 cm^{-1}	1274.00 cm^{-1}
				1235.74 cm^{-1}
F-8	3212.97 cm^{-1}	1164.24 cm^{-1}	1345.75 cm^{-1}	1273.34 cm^{-1}
				1235.89 cm^{-1}
F-9	-	-	1346.61 cm^{-1}	1272.14 cm^{-1}
				1235.25 cm^{-1}

Table 4: Model fitting values of F-1 toF-9 microsponge formulations and VF-1 to VF-3microsponge converted gels.

	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
				Model fitting values					
Zero order	0.1813	0.2554	0.3737	0.3804	0.4679	0.5394	0.2577	0.2075	0.3094
1st order	0.8667	0.85	0.8502	0.9391	0.9254	0.923	0.9024	0.8502	0.8496
Matrix	0.9242	0.9291	0.9395	0.9418	0.9517	0.9603	0.9302	0.9257	0.9335
Peppas	0.9855	0.9867	0.9843	0.99	0.9895	0.9884	0.9894	0.9866	0.9855
Hix.crow	0.7539	0.7421	0.7539	0.8467	0.8401	0.8462	0.7971	0.7393	0.7463
			Parameters for Korsemeyer Peppas Equation						
n	0.3461	0.3492	0.371	0.3624	0.3818	0.4044	0.3456	0.3465	0.3585
k	44.2487	42.0896	39.6719	46.707	43.416	40.7288	46.3226	43.0165	40.996
Best fit	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas
		VF-1			**VF-2**			**VF-3**	
				Model fitting values					
Zero order		0.9376			0.9158			0.8729	
1st order		0.9883			0.9895			0.9797	
Matrix		0.9886			0.9957			0.9969	
Peppas		0.9822			0.9941			0.9893	
Hix.crow		0.9857			0.9809			0.9698	
			Parameters for Korsemeyer Peppas Equation						
n		0.6954			0.5862			0.5259	
k		21.5043			25.4351			29.6556	
Best fit		Matrix			Matrix			Matrix	

Table 5: Skin irritation data of microsponge gels.

For. Code	Score after (days)						Mean score
	1	2	3	4	5	6	
Std	0.666	0	2	2.66	1.66	2	1.4976

For. Code	Score after (days)				Mean score
	2	3	5	7	
VF-1	0	2.0	1.59	2.4	1.4975
VF-2	0.1	2.1	1.57	2.2	1.4925
VF-3	0.12	2.2	1.51	2.1	1.4825

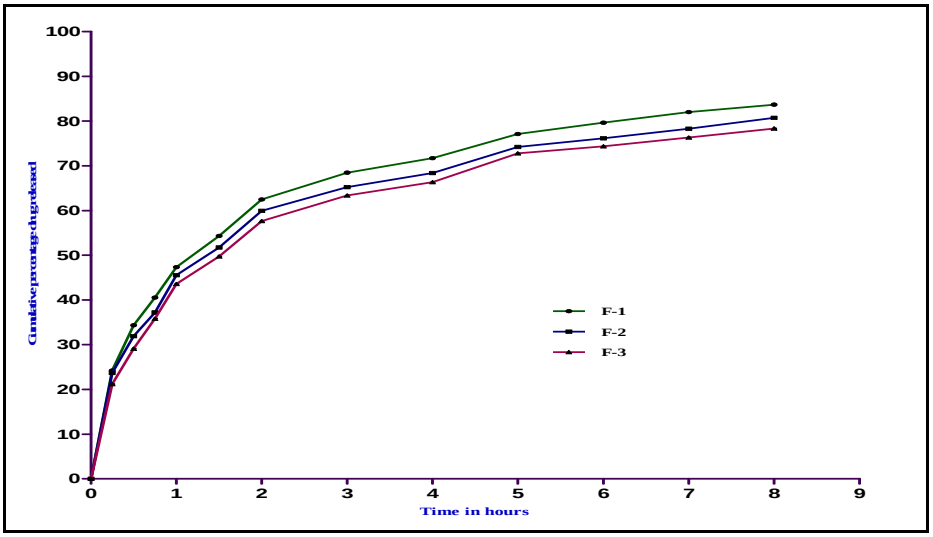

Fig.4. Comparative dissolution profiles of F-1, F-2 and F-3 microsponge formulations.

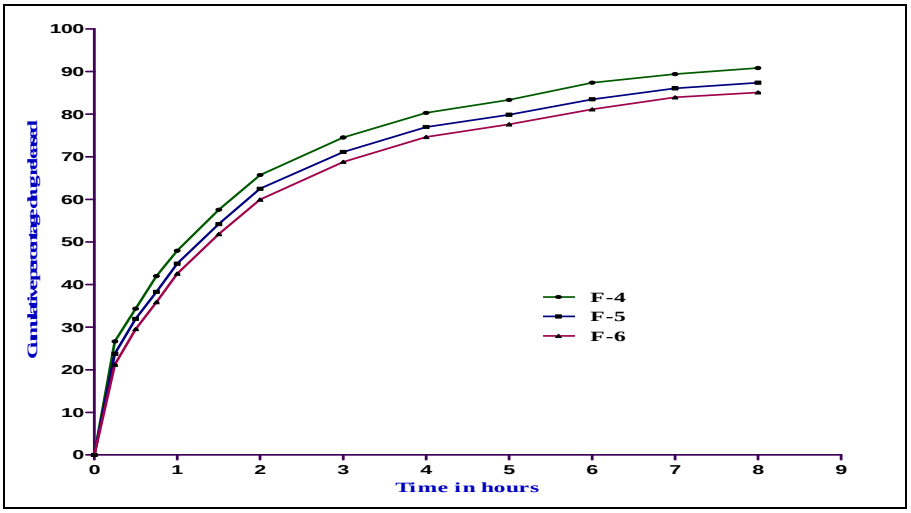

Fig.5. Comparative dissolution profiles of F-4, F-5 and F-6 microsponge formulations.

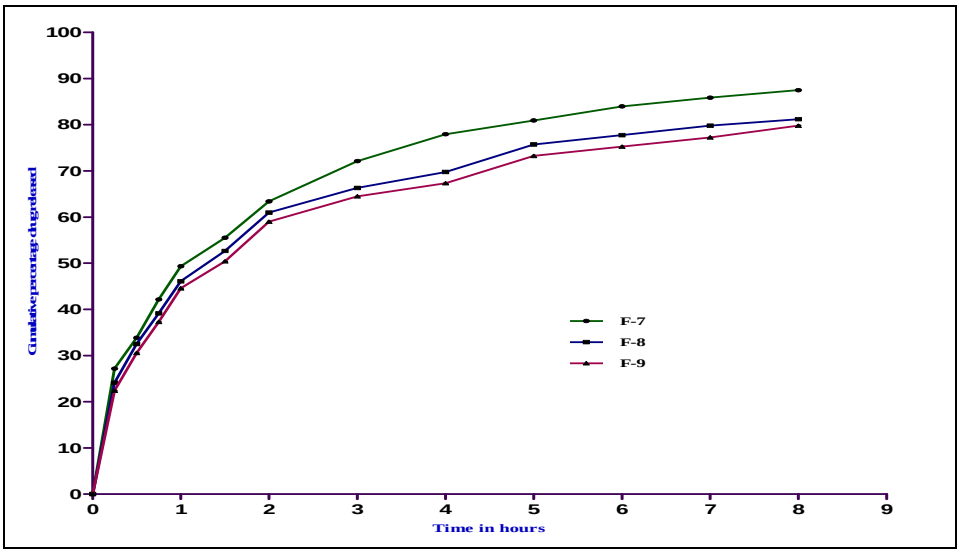

Fig.6. Comparative dissolution profiles of F-7, F-8 and F-9 microsponge formulations.

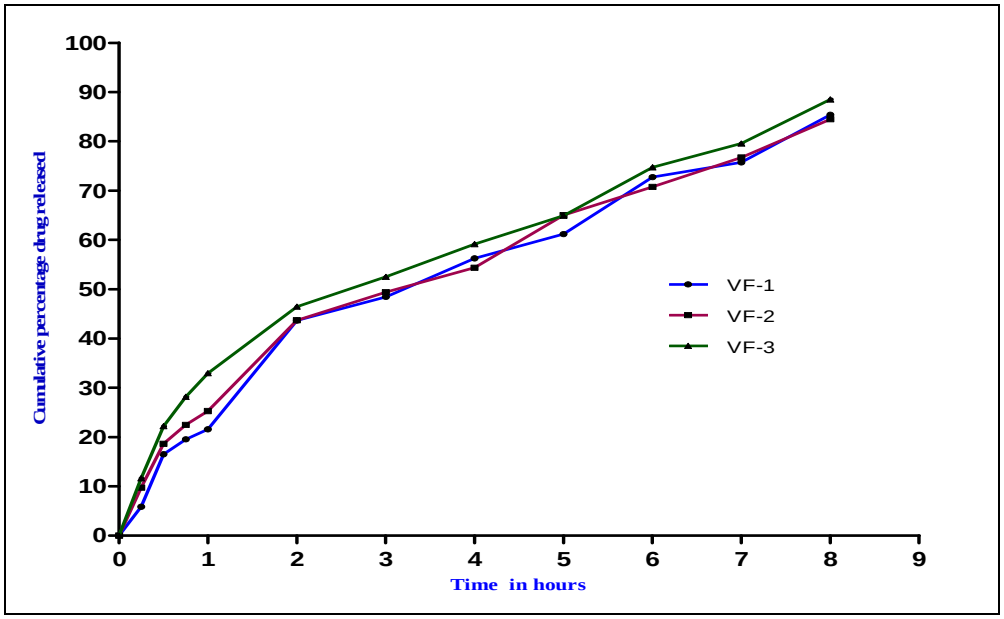

Fig.7. Comparative dissolution profiles of VF-1,VF-2 and VF-3 microsponge gel formulations.