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Formulation and evaluation of colon specific drug delivery system containing ketorolac microsponge oral tablet

Arindam Chatterjee[1], Jitendra Kumar[2], Sunil Sain[3], Rakesh Kumar Gupta[4], Vikash Agarwal[5], Sumit Alwani[6*]

[1] *Associate Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, India.*
[2] *Sr. Executive at Medicef Pharma, Solan, Baddi.*
[3] *Assistant Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, India.*
[4] *Professor, Department of Pharmaceutical Analysis, Jaipur College of Pharmacy, Jaipur, India.*
[5] *Professor, Department of Pharmaceutical Chemistry, Jaipur College of Pharmacy, Jaipur, India.*
[6] *Student, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, India.*

***Corresponding Author: Sumit Alwani**

ABSTRACT

The present study was mainly aimed to formulate the Ketorolac loaded microsponge based colon targeted tablet for treatment of colon specific disease. The major excipient used in this study was Eudragit S-100, and polymeric microsponges were utilized for delivery of drug. The drug was loaded into microsponges those were fabricated by using quasi emulsion solvent diffusion technique and hence evaluated for different parameters like, particle size, production yield, entrapment efficiency, surface morphology and micromeritics properties in orderly. The evolution results were shown that good production yield, drug entrapment efficiency and spherical morphology. Later the microsponge based tablet was also prepared by using direct compression method along using the excipients like, lactose and then evaluated with respect to drug content and *in-vitro* drug release kinetics as well. The formulation were showed desirable amount of drug (more than 90 %). The drug release of formulation shows zero order kinetics with diffusion-controlled mechanism. That why the present study can be considered as a novel approach for colon targeted delivery of Ketorolac.

Keywords: Microsponge, drug release

INTRODUCTION

Microsponges are porous microspheres contain a complex network of interconnecting voids with a noncollapsible structure. These systems can absorb a wide range of active ingredients such as emollients, volatile oils, sunscreens, perfumes, and anti-infective and antifungal agents. The release rate of the active ingredients can be determined before they are entrapped in the microspheres.[1] Depending on several factors, such as pore diameter, extent of cross-linking of the polymers, concentration difference of the active ingredient between the microspheres and the vehicle in which these spheres resides. The topical agent formulation with this system can be prepared in many different forms such as a gel, cream, or lotion.[2] The active ingredients diffuse out of the spheres into the vehicle and then onto the skin, while applying the formulation topically to the desired area of the skin. The release can be initiated by many release triggers, including pressure and temperature changes and moisture.[3] The microsponges cannot pass through to the stratum corneum because of their size, so they retained on the skin surface, releasing slowly the active ingredients over a period of time. The rate of release associated with MDS provides more control, which potentially has an impact on the intensity of skin irritancy provoked by the topical agent.[4] polymeric microspheres that are mostly used for prolonged topical administration,[5] microsponges are designed to deliver a pharmaceutically active ingredient efficiently a minimum dose and also to enhance stablilty,[6] reduce side effects,[7] and modify drug release profiles.[8] Many of conventional delivery system require high concentration of active ingredient to be incorporated for effective therapy because of their low efficiency as delivery system.[9] Thus the needs exist for delivery system to maximize the period of time that an active ingredient is present.[10] The microsponge- based polymeric microspheres unequally fulfil such requirements.[11] Microsponges are prepared by several methods utilizing emulsion system[12] as well as by suspension polymerization in a liquid - liquid system.[13] The most common emulsion system used is oil –in – water[14] with the microsponges being produced by the emulsion solvent diffusion method.[15]

MATERIALS AND METHODS

The drug Ketorolac IP was a kind gift from Zydus Gujrat, Eudragit S-100 and Kollidon K90 were obtained from Loba Chemicals Private Limited, Magnesium stearate was obtained from Fisher Scientific, Mumbai, Lactose and Polyvinyl alcohol were obtained from Merck Limited, Mumbai.

Preparation of KETOROLAC loaded microsponges

The KETOROLAC loaded polymeric microsponges were fabricated by quasi emulsion solvent diffusion technique[16] using various ratios of Eudragit S 100 polymer.[17] The internal phase was prepared by dissolving weighed quantities of Eudragit S-100 and dibutyl phthalate in ethanol: dichloro- methane (1:1).[18] Dibutyl phthalate was included in formulation to improve the plasticity of the polymer.[19] Further KETOROLAC was dissolved in prepared polymeric solution through ultrasonication at 35 °C. This mixture was theninjected into an aqueous solution of PVA with continuous stirring rate 500 rpm for 60 min.[20] The microsponges were formed due to the evaporation of volatile solvent from the system. Prepared microsponges were then filtered, washed with distilled water and finally subjected to drying at 40 °C for 12 h in hot air oven.[21] The prepared microsponges then weighed to determine production yield. The various formulation batches of microsponges were prepared by varying drug: polymer ratios[22] as per Table1.

Table 1: Composition of KETOROLAC microsponge batches (F1-F6)

Ingredients	F1	F2	F3	F4	F5	F6
KETOROLAC: Eudragit S-100 (mg)	1:1	1:2	1:3	1:4	1:5	1:6
Ethanol: Dichloromethane (ml)	5	5	5	5	5	5
Dibutylphthalate (% w/v)	1	1	1	1	1	1
Polyvinyl alcohol (% w/v)	0.05	0.05	0.05	0.05	0.05	0.05
Water (ml)	100	100	100	100	100	100

RESULT AND DISCUSSION

Infrared spectral analysis

The IR spectrum was used to determine the interaction of the drug with the polymers used.[23] The infrared spectra of samples were obtained using a spectrophotometer (FTIR,[24]Jusco, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into discs using hydraulic press before scanning from 4000 to 400 cm^{-1}.[25]

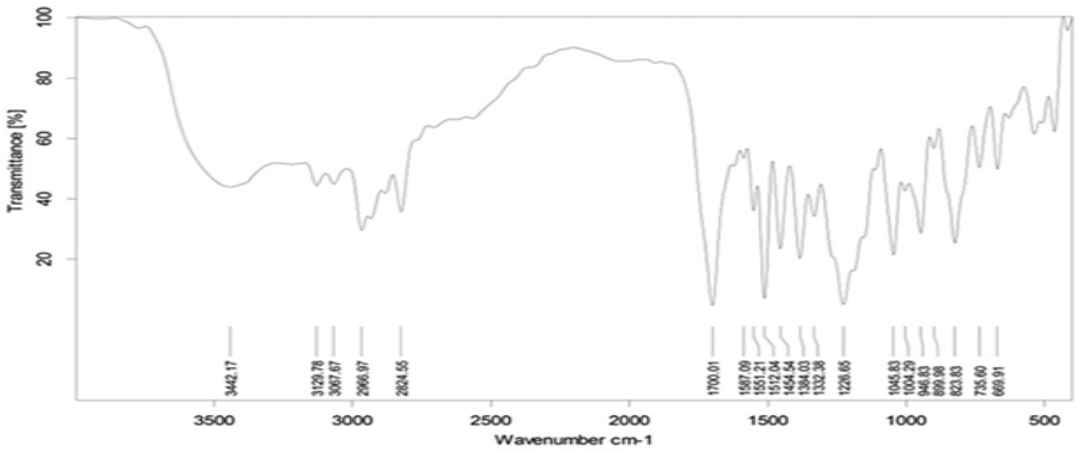

Fig 1: FTIR Spectrum of Ketorolac

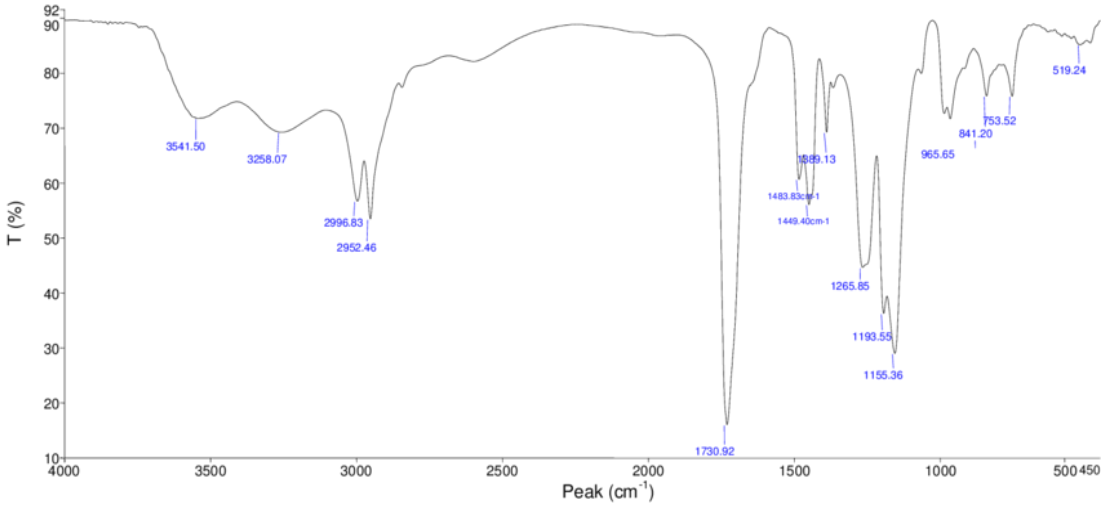

Fig 2: FTIR Spectrum of Eudragit RS 100.

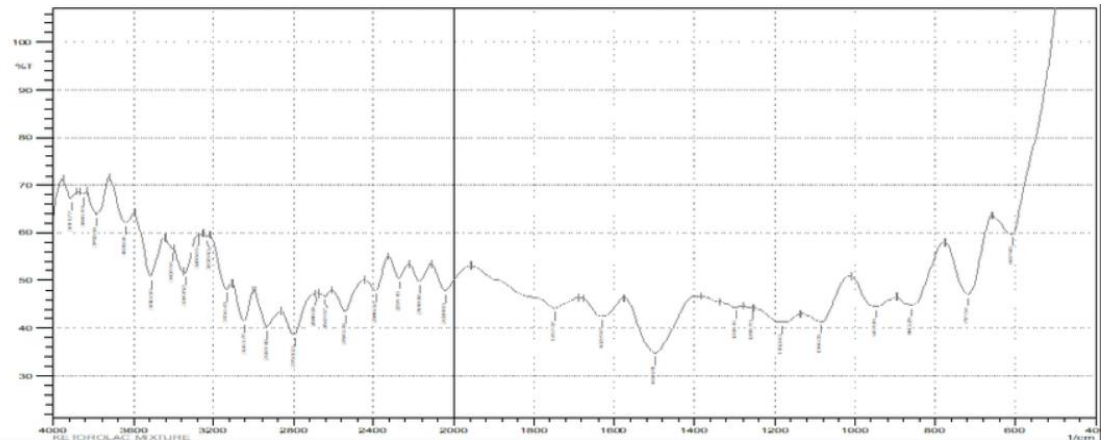

Fig 3: FTIR Spectrum of Ketorolac with Eudragit RS 100

There was no change in the functional peaks of drug when studied the FTIR spectra,[26] and the physical mixture of Ketorolac and Eudragit RS 100 shows no incompatibility as all functional group peaks were clearly identified in the spectra of the physical mixture of Ketorolac with Eudragit RS 100.[27]

Differential Thermal Analysis (DTA)

The physical state of drug in the microspheres was analyzed by Differential Thermal Analyzer (Mettler-Toledo star 822e system,[28] Switzerland). The thermo grams of the samples were obtained ata scanning rate of 10°C/min conducted over a temperature range of 25-220°C, respectively.[29]

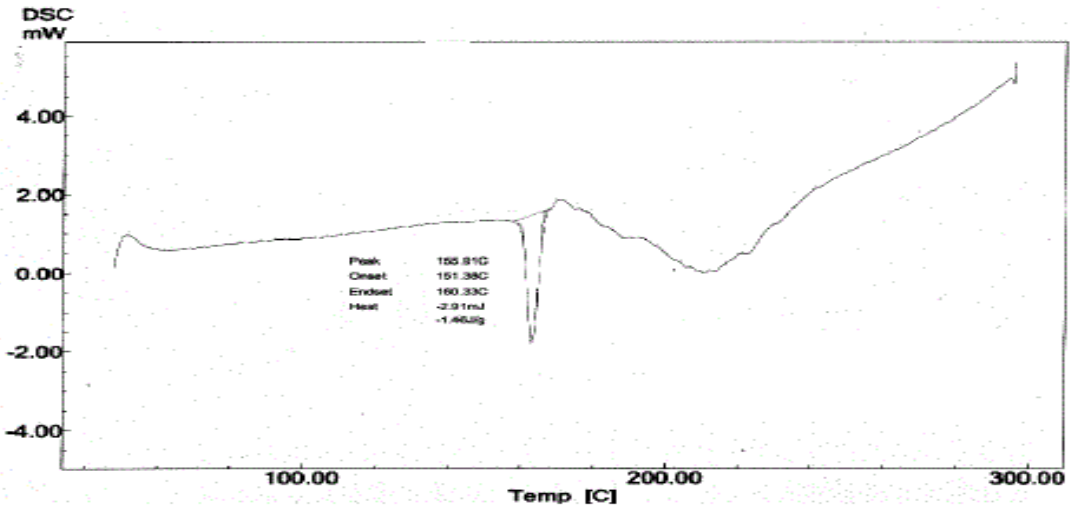

Fig 4: DTA analysis of pure drug Ketorolac with polymer Eudragit RS 100

Production yield

The estimated production yield of all five batches of (Ketorolac Tromethamine) KTM loaded microsponges. The selected drug: polymer ratios were found to affect the production yield.[29] With increase in drug: Polymer ratio from 1:1 (F1) to 1:6 (F6), the production yield was found to increase. The production yield for formulation batch F1 i.e. drug: Polymer ratio 1:1 was very low, i.e. 28.54% while that with drug Polymer ratio 1:6 (F6) was 79.58%. The drug: polymer can possibly change the rate of diffusion of volatile solvent in aqueous medium while formation of microspheres.[30] The increase in polymer concentration was reported to reduce diffusion rate of volatile solvent to the aqueous phase, which can provides more time for formation of droplet following improved yield.

Table 2: Product yield

	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
% yield	28.54±1.79	44.85±2.54	51.13±2.69	68.29±4.56	72.57±3.89	79.58±4.19

microsponges: excipient blend (n=3).

Actual drug content and drug encapsulation efficiency

The actual amount of drug encapsulated in microsponges was found to be lesser than theoretical amount of drug included in formulation, because drug encapsulation efficiency is less than 100%.[30] The encapsulation efficiencies were in the range of 85.35 – 95.74% as mentioned in Table. The less entrapment efficiency of drug is may be due to dissolution of fraction of drug in aqueous phase which eventually loss.[31]

Table 3: Actual drug content and drug encapsulation efficiency

	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Actual drug content	48.37±0.08	32.34±0.06	21.37±0.08	16.84±0.04	13.52±0.16	11.52±0.03
Drug Encapsulation efficiency	95.74± 0.02	94.62± 0.01	91.28± 0.02	90.12 ± 0.03	87.85± 0.12	85.35± 0.09

microsponges: excipient blend (n=3).

Particle size and surface morphology

The particle size of drug loaded microsponges was found to be in the range of 32.74 - 89.34 µm.[32] The photon correlation spectroscopy revealed that particle size has increased with increase in drug: Polymer ratio.[33] It was because of the fact that with increase in drug: polymer ratio the more amount polymer was available for formation of microsponges which eventually increase polymer wall thickness which led to the more particle size of microsponges. The SEM image of microsponge revealed spherical shape of microsponges.[34]

Table 4: Particle size

	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Particle Size	32.74±3.72	46.12±5.47	63.19±5.89	68.57±6.75	87.34±8.19	89.34±8.19

microsponges: excipient blend (n=3).

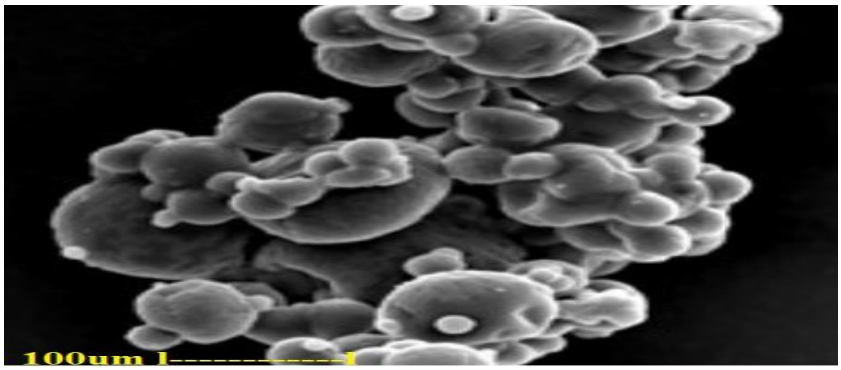

Fig 5: SEM picture of formulation

In vitro drug release study

The data obtained from the in vitro drug release[34] study are represented in table for formulationsF1, F2, F3 and in table 5 for formulation F4,F5,F6.

The in-vitro dissolution profile for the various Ketorolac tablet formulations is givenbelow in Fig. 20 for formulation F1, F2 ,F3 and in Fig.. for formulations F4, F5, F6**.**

Table 5: Cumulative percentage in-vitro drug release of Ketorolac tablet formulations F1,F2,F3

Time (min)	F1	F2	F3
15	10.11±0.77	15.51±0.54	11.39±0.66
45	23.32±0.56	26.79±0.34	21.88±0.15
60	30.62±0.65	41.57±1.22	36.63±2.02
120	40.01±0.97	62.91±1.34	55.15±1.01
180	51.23±0.78	76.98±0.17	67.29±0.81
240	66.61±0.51	83.62±0.19	70.31±0.14
300	74.41±0.18	93.11±0.99	74.05±0.22
360	78.32±0.88	98.25±0.23	83.50± 0.12

Table 6: Cumulative percentage in-vitro drug release of Ketorolac tablet formulations F4,F5,F6

Time (min)	F4	F5	F6
15	15.77±1.22	14.38±1.34	12.41±0.79
45	23.12±1.34	29.11±1.77	25.62±0.56
60	41.23±0.36	55.31±0.99	46.97±1.11
120	52.79±1.91	74.92±2.01	61.66±1.04
180	61.44±0.87	80.96±1.31	75.32±0.67
240	72.52±0.48	91.73±0.22	77.81±1.22
300	77.92±0.53	93.41±1.23	81.33±0.33
360	81.34±0.65	96.54±0.88	87.32±1.04

Ex vivo drug permeation study

The drug permeation data for the various Ketorolac tablet formulations is given below intable 7 for formulation F1, F2, F3 and in table 20 for formulations F4, F5, F6. The ex vivo drug permeation profile for the various Ketorolac tablet formulations isgiven below in Fig. for formulation F1, F2, F3 and in Fig. for formulations F4,F5,F6**.**

Table 7: Cumulative percentage drug permeation for Ketorolac tabletformulations F1, F2, F3

Time (min)	F1	F2	F3
15	8.93±1.28	11.2±1.22	7.32±1.24
45	20.13±1.45	25.42±0.56	21.01±0.63
60	29.86±1.71	31.3±0.34	30.51±1.05
120	36.23±2.04	49.71±2.01	40.13±1.12
180	47.51±2.11	66.32±1.73	56.91±0.89
240	56.31±0.66	79.52±0.77	60.91±0.67
300	68.92±0.79	83.08±0.225	79.70±0.35
360	72.63±0.71	96.63±0.23	83.55±0.78

Table 8 : Cumulative percentage drug permeation for Ketorolac tablet formulations F4, F5,F6

Time (min)	F4	F5	F6
15	9.58±0.64	12.81±1.55	9.77±0.89
45	16.8±1.33	28.52±1.79	17.12±0.78
60	19.35±1.92	36.71±0.89	21.33±1.76
120	28.3±0.91	59.21±0.86	39.82±1.54
180	47.17±0.75	71.39±0.78	53.27±1.03

240	59.5±0.47	82.4±1.27	61.8±1.07
300	70.23±0.59	89.51±1.11	74.59±0.74
360	79.54±1.63	95.81±0.36	81.03±0.97

Drug release kinetics for the tablet formulations

Out of all the prepared formulation, F2 was selected as optimized formulation as it gave the best results for cumulative percentage drug release.[35] The drug release kinetics for the optimized formulation (F2) was calculated and the results obtained are represented in table 9. The zero order profile, first order profile, Higuchi profileand Korsmeyer-Peppas[36] plot is represented in Figures.

Table 9: Release kinetics and mechanisms of Ketorolac tablet of optimized formulation (F4)

Formulationcode	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-Crowell(R^2)	Korsmeyer-Peppas		Possible drugrelease mechanism
					(R^2)	N	
F4	0.9908	0.911	0.9835	0.799	0.9465	0.6798	Non-Fickian transport

DISCUSSION

Precompressional formulation parameters

The standard calibration of pure drug proved that Ketorolac supplied was of pharmacopoeiastandards.
From the obtained FTIR peaks it can be concluded that the physical mixture of the drugKetorolac does not show any major interactions with formulation excipients.

Weight variation

Values of weight variation are found to be within the permissible limits of conventional oraltablets stated in the I.P. Weights of the tablets varied between 197.3-202.1mg with deviation in the range of 1.91-3.62. The extreme variation could have been the result of mishandling of the tablet weights during punching process.

Thickness

The average thickness of Ketorolac tablets is found to be quite uniform with minimum variation.
The thickness of various tablet preparation were observed in the range of 3.60mm to 3.98mm with standard deviation in the range 0.023 to 0.091.

Hardness and friability

The hardness of the prepared Ketorolac tablet lies in the range of 5.24 to 5.02 g/cm^2 withthe standard deviation in the range of 0.09 to 0.55. Also the friability lies in the range of 0.025% to 0.520%Friability is not more than 1% for any formulation. The hardness of Ketorolac tablets is low, but the friability data suggests that the tablets are quite robust enough to withstand the normal handing.

Stability Studies

The stability studies of prepared formulations revealed no significant changes in the physical parameters when stored at temperature and humidity conditions of 40 ± 2°C/75 ± 5% RH. Samples were withdrawn and retested for drug content after intervals of 7, 15, 30, 60, and 90 days. Percent drug content was found in all the prepared formulations ranging from 95.21 ± 0.41 to 97.61 ± 0.37, indicating that no significant reduction in the content of the active drug was observed over a period of 3 months; the percent drug contained is found within a specified limit of USP. Therefore, there was no evidence of degradation of drug quantity.

SUMMARY

In the present work, an attempt was made to formulate and evaluate the Ketorolac microsponges and then compress it into tablet to evaluate the various tablet parameters and the results are as below,
The standard calibration of pure drug proved that Ketorolac supplied was of pharmacopoeiastandards. From the obtained FTIR peaks it can be concluded that the physical mixture of the drugKetorolac does not show any major interactions with formulation excipients.
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The aim of the present study was achieved as to formulate Ketorolac encapsulated microsponge based colon targeted tablet. The Eudragit S-100 polymeric microsponge revealed acceptable production yield, drug content and drug entrapment efficiency with spherical shape. The drug release profile followed zero order kinetics with diffusion-controlled release mechanism. Thus, microsponge based colon targeted tablet could be novel approach for colon specific delivery of Ketorolac.

REFERENCES

1. Rehan U, Sansare V. Design, fabrication and evaluation of ketorolac tromethamine loaded microsponge based colon targeted tablet. Adv Pharm. 2020 6(2) 09–13.
2. Mahant S, Kumar S, Nanda S, Rao R. Microsponges for dermatological applications: perspectives and challenges. Asian J Pharm Sci. 2020 May;15(3):273-91. doi: 10.1016/j.ajps.2019.05.004, PMID 32636947.
3. Obiedallah MM, Abdel-Mageed AM, Elfaham TH. Ocular administration of acetazolamide microsponges in situ gel formulations. Saudi Pharm J. 2018 Nov;26(7):909-20. doi: 10.1016/j.jsps.2018.01.005, PMID 30416345.
4. Bhatia M, Saini M. Formulation and evaluation of curcumin microsponges for oral and topical drug delivery. Prog Biomater. 2018 Sep;7(3):239-48. doi: 10.1007/s40204-018-0099-9, PMID 30242738.
5. Pawar AP, Gholap AP, Kuchekar AB, Bothiraja C, Mali AJ. Formulation and evaluation of optimized oxybenzone microsponge gel for topical delivery. J Drug Deliv. 2015;2015:261068. doi: 10.1155/2015/261068, PMID 25789176.
6. Li SS, Li GF, Liu L, Jiang X, Zhang B, Liu ZG et al. Evaluation of paeonol skin-target delivery from its microsponge formulation: in vitro skin permeation and in vivo microdialysis. PLOS ONE. 2013 Nov 20;8(11):e79881. doi: 10.1371/journal.pone.0079881, PMID 24278204.
7. Bhagwat RR, Vaidhya IS. Novel drug delivery systems: an overview. Int J Pharm Sci Res. 2013;4(3):970-82. doi: 10.13040/ijpsr.0975-8232.4(3).970-82.
8. Inamuddin, Asiri, A, & Mohammad, A. 2018. Applications of nanocomposite materials in drug delivery (pp. 509-73). Woodhead Publishing.
9. Bhowmik D, Gopinath H, Kumar PB, Duraivel S, Kumar Sampth KP. Controlled drug delivery systems. J Pharm Innov. 2012;1:24-32.
10. Patil RS, Kemkar VU, Patil SS. Microsponge drug delivery system: A Noveldosageform Am. J Pharm Tech Res. 2012;2(4).
11. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Martin GP, Nokhodchi A. The microspongedelivery system of benzoyl peroxide: preparation, characterization and release studies. Int J Pharm. 2006;308(1-2):124-32. doi: 10.1016/j.ijpharm.2005.11.001, PMID 16359833.
12. Bhatt V, Karakoti R, Singh A, Sharma D. Microsponges a novel approach for drug delivery system; Published in 2014.
13. Srivastava R, Kumar D, Pathak K. Colonic luminal surface retention of meloxicam microsponges delivered by erosion based colon-targeted matrix tablet. Int J Pharm. 2012;427(2):153-62. doi: 10.1016/j.ijpharm.2012.01.036, PMID 22306039.
14. Panday P, Shukla N, Sisodiya D, Jain V, Mahajan SC. Design and characterization of Microsponge loaded Controlled release epicutaneous gel of lornoxicam. Appl Med Res. 2015;1(1):16-21. doi: 10.5455/amr.20150127052147.
15. Nevine s Abdel malak, Shahira Menshawe , a new topical fluconazole microsponge loaded hydrogel: preparation and characterization. Int J Pharm Pharm Sci. 2012;4;Suppl 1:461-8.
16. Vijay R, Bajaj A, Madan M. Development of microsponges for topical delivery of Mupirocin. AAPS PharmSciTech. 2019;10(2):402-9.

17. Buddhabhushan V, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. Microsponges: A novel strategy for drug delivery system. J Adv Pharm Technol Res. 2019;1(3):283-90.
18. Yadav V, Ghanawat PB, Welankiwar AS, Kumar J, Chakole RD. Microsponge: A novel new drug delivery system: a review. Int J Adv Pharm. 2017;2(6):63-70.
19. Ankaj K, Rohit B, Amit S, Pankaj S. Areview onmicrosponges drugdeliverysystem.2014;3(1):177-81.
20. Makwana RPH, Patel V. Photostability enhancement of miconazole nitrate by microsponge formulation. Int J Curnt Trnd Pharm Res. 2014;2(3):437-58.
21. Malode S, Bhaskar GD. Formulation, development and in-vitro evaluation of terbinafine HCl microsponge gel. Int J Pharm Res Sci. 2014;6(7):84-91.
22. Ramani G, Anitha M, Aparna A, Keerthi KB, Murthy TEG. Design and Development of hydroxyzine hydrochloride controlled release tablets based on microsponge technology.carib. J Sci Technol. 2013;1:172-84.
23. Karthika R, Elango K, Ramesh KK, Rahul K. Formulation and Evaluation of lornoxicam microsponge tablet for the treatment of arthritis. Int J Pharminnov. 2013;3(2):29-40.
24. Namrata J, Vruti P, Siddesh M, Gaurav B, Manisha K, Vilasrao K. Microsponge delivery system. JSIR J. 2013;2(6):177-81.
25. Mahajan AG, Leena GS, Atul CL, Sima SP, Prabha MR. Formulation and evaluation of microsponge drug delivery system using indomethacin. Int Res J Pharm. 2011;2(10):64-9.
26. Vikas J, Ranjit S. Development and characterization of Eudragit RS100 loaded microsponges and its colonic delivery using natural polymers. Acta Pol Pharm Drug Res. 2010;67(4):407-15.
27. Rasika DB, Rao sahib SS, Fatima JS, Kishore SS. Development of colon specific drug delivery of aceclofenac by using effective binder system of ethyl cellulose. IntJofPharmaandBiosci. 2010;1(3):1-5.
28. Orlu M, Cevher E, Araman A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J Pharm. 2006 Aug 2;318(1-2):103-17. doi: 10.1016/j.ijpharm.2006.03.025, PMID 16687222.
29. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30. PMID 10942969.
30. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. Int J Pharm Sci Res. 2012;3(3):659-81.
31. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014;28(2):81-97. doi: 10.7555/JBR.27.20120136, PMID 24683406.
32. Shaikh R, Raj Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011;3(1):89-100. doi: 10.4103/0975-7406.76478, PMID 21430958.
33. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in mucoadhesive drug delivery system: a brief note. Des Monomers Polym. 2009;12(6):483-95. doi: 10.1163/138577209X12478283327236.
34. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery: a promising option for orally less efficient drugs. J Control Release. 2016;114(9):15-40.
35. Lieberman HA, Lachman SB. Pharmaceutical Dosage forms: tablets. 2nd ed. Vol. 1. New York: Marcel Dekker; 1989.
36. Patel PS, Parmar AM, Doshi NilangS, Patel HV, Patel RR. Buccal drug delivery system: a review. Int J Drug Dev Res. 2013;5(3):35-48.