IJPSR (2021), Volume 12, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 June 2020; received in revised form, 10 October 2020; accepted, 04 May 2021; published 01 June 2021

TO STUDY THE EFFECT OF NATURAL POLYMER ON THE RELEASE OF OSMOTIC TABLET FOR COLON SPECIFIC DRUG DELIVERY SYSTEM

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Keywords:

Pectin, Chitosan dexamethasone, Eudragit L-100-55, osmotic tablet, Colon targeting

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ABSTRACT: Controlled and targeted drug delivery system is more advantages than conventional dosage in various aspects. In the case of treating colonic disorders such as inflammatory bowel disease, the drugs do not reach the site of action in appropriate concentration. Thus there is a need to develop effective and safe therapy for the treatment of these colonic disorders, using site-specific drug delivery approach. The present study was aimed to develop microbially triggered osmotic pump so as to achieve colon specific delivery of dexamethasone. The microbially triggered colon-targeted osmotic pump (MTCT-OP) based tablets are prepared by using two types of polymers chitosan and pectin. The tablet is formulated by using directly compressible method, which consists of an osmotic core (drug and chitosan with organic acid as excipient) and (drug and pectin with organic acid as excipient) with an inner semi-permeable membrane layer composed of the mixture of cellulose acetate and chitosan powder and an outer enteric-coating layer of eudragit® L100-55. Then a comparative study of this formulation was done. It was found that shows F4S2E1 better results than P4M2C1. The % drug content in the case of F4S2E1 and P4M2C1 was found 99.02 ± 0.03 and 98.68 ± 0.04, respectively. The cumulative % drug release study showed that maximum drug release was found in the case of F4S2E1 and P4M2C1 was 99.027 ± 0.47 and 95.027 ± 0.47 respectively at 24 h. The results from various evaluations show that formulation code F4S2E1 and P4M2C1 are found to be optimized batch. In both formulations, F4S2E1 shows better results in all parameters. The drug was almost completely released in SCF after 24 h.

INTRODUCTION: The oral route is the most convenient and preferred route for the drug delivery system but the colon-targeted drug delivery system (CDDS) has been more focus for studies in recent years due to its potential to improve treatment of local diseases affecting the colon, with minimum systemic side effects [5]. Some examples of disease states which impact the colon include [6] Crohn's disease (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(6).3410-17

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(6).3410-17

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, and systemic delivery of drugs [7]. The aim of a targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site [8].

It is suitable and required for the drugs having instability, low solubility and short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index [9]. Targeting may provide maximum therapeutic activity (by preventing degradation or inactivation of the drug). Meanwhile, it can also minimize adverse effects, the toxicity of potent drugs by reducing dose [10].

The oral route is the most convenient and important method for the administration of drugs for systemic effect. Drug delivery systems for treating colonic disorders such as inflammatory bowel disease are failing as the drugs do not reach the site of action in appropriate concentration [11]. Thus, there is a need to develop effective and safe therapy for the treatment of these colonic disorders, using a site-specific drug delivery approach [12].

However, the development of such a system is a challenging task for pharmaceutical technologists [13]. The available conventional dosage forms are not very much effective in the treatment of diseases as they are absorbed in the upper gastrointestinal tract, which may lead to many adverse effects [14]. Dexamethasone is a drug of choice to treat inflammatory bowel disease [15]. It is well documented that dexamethasone can be completely absorbed in the upper gastrointestinal tract when free dexamethasone is simultaneously administered orally [16]. This rapid and complete absorption of dexamethasone can easily cause systemic side effects like osteoporosis, depression, insomnia, dyspepsia, abdominal distension, congestive heart failure in susceptible patients [16].

The present study was aimed at developing a microbially triggered osmotic pump so as to achieve colon-specific delivery of dexamethasone [17]. This could help in the effective treatment of inflammatory bowel disease for a prolonged time at site of action and reduction in dosing frequency [18]. Moreover, this may increase patient compliance and reduction in adverse effects.

MATERIALS AND METHODS:

Materials: Dexamethasone was obtained as a gift sample from R. P. Traders, Delhi. Chitosan (deacetylation degree ≥75 %) and triethyl citrate (TEC) were purchased from Sigma-Aldrich Co. Ltd. Citric acid, and cellulose acetate (CA, 53.5–56 wt% acetyls content) was procured from Qualigens Fine chemicals (Mumbai). All reagents were of A. R. grade.

Formulation Development: Dexamethasone was pre-mixed with a small amount of chitosan and followed by mixing of other ingredients. The resultant powder was directly compressed into tablets [19].

Then a coating of cellulose acetate in acetone containing of pore-forming agent (chitosan) was carried out in pan coater provided hot air blower (Macro Scientific works, New Delhi, stainless steel pan, 50 cm diameter). After coating, the tablets were dried for 12 h at 50 °C. Then different concentrations of Eudragit® L100-55 were used to coat on the surface of microporous semipermeable membrane [20]. The surface of formulated MTCT-OP tablet had a smooth and uniform appearance [21]. The same steps were followed for pectin tablets. The process is done in the following steps.

Preparation of Core Tablets: Dexamethasone was pre-mixed with a small amount of chitosan and pectin respectively by speculation, followed by mixing manually for 10 min with the remaining chitosan and other ingredients [22]. The resultant powder mixture was sieved through 100 mesh screen and directly compressed into tablets using 8.0 mm standard concave punches on a single punch tablet machine [23]. The core compositions are listed in **Table 1** and **2.**

TABLE 1: COMPOSITION FOR CORE TABLETS WITH CHITOSAN POLYMER

S. no.	Ingredients (mg/Tablet)	Core Code				
		F1	F2	F3	F4	F5
1	Dexamethasone	0.5	0.5	0.5	0.5	0.5
2	Chitosan	60	30	30	33	24
3	Citric acid	0.0	30	60	66	48
4	SMCC	54	54	24	15	42
5	Mag. stearate	0.6	0.6	0.6	0.6	0.6

TABLE 2: COMPOSITION FOR CORE TABLETS WITH PECTIN POLYMER

S. no.	Ingredients (mg/Tablet)	Core Code				
		P1	P2	P3	P4	P5
1	Dexamethasone	0.5	0.5	0.5	0.5	0.5
2	Pectin	60	30	30	33	24
3	Citric acid	0.0	30	60	66	48
4	SMCC	54	54	24	15	42
5	Mag. stearate	0.6	0.6	0.6	0.6	0.6

Microporous Semipermeable Membrane Coating: Cellulose acetate in acetone containing different levels of pore-forming agent (chitosan) was used as coating formulation.

After coating, the tablets were dried for 12 h at 50 ºC to remove residual solvent [23]. The microporous semipermeable coating formulations used are listed as shown in **Table 3** and **4.**

TABLE 3: MICROPOROUS SEMIPERMEABLE MEMBRANE COATING IN CHITOSAN FORMULATIONS

S. no.	Formulation Code	Coating Composition (%)		
		Chitosan	CA	TEC
1	S1	30	45	25
2	S2	25	50	25
3	S3	20	55	25
4	S4	15	60	25

TABLE 4: MICROPOROUS SEMIPERMEABLE MEMBRANE COATING IN PECTIN FORMULATIONS

S. no.	Formulation Code	Coating Composition (%)		
		Pectin	CA	TEC
1	M1	30	45	25
2	M2	25	50	25
3	M3	20	55	25
4	M4	15	60	25

Enteric Coating: Different concentrations of Eudragit® L100-55 were used to coat on the surface of microporous semipermeable membrane [24]. The surface of MTCT-OP tablet had a smooth and uniform appearance. Coated tablets were dried for 4 h at 40 ºC. Total weight gain by different coating solutions was 5%, as shown in **Table 5-6** and **Fig. 1-2.**

TABLE 5: ENTERIC COATING IN CHITOSAN FORMULATION

S. no.	Formulation Code	Coating Composition			
		Eudragit® L100-55(gm)	I.P.A. (ml)	Acetone (ml)	TEC (ml)
1	E1	8	73	42.2	1.5
2	E2	6	73	44.7	1.5
3	E3	4	73	47.1	1.5

TABLE 6: ENTERIC COATING IN PECTIN FORMULATION

S. no.	Formulation Code	Coating Composition			
		Eudragit® L100-55(gm)	I.P.A. (ml)	Acetone (ml)	TEC (ml)
1.	C1	8	73	42.2	1.5
2.	C2	6	73	44.7	1.5
3.	C3	4	73	47.1	1.5

FIG. 1: ENTERIC COATED CHITOSAN BASED TABLET

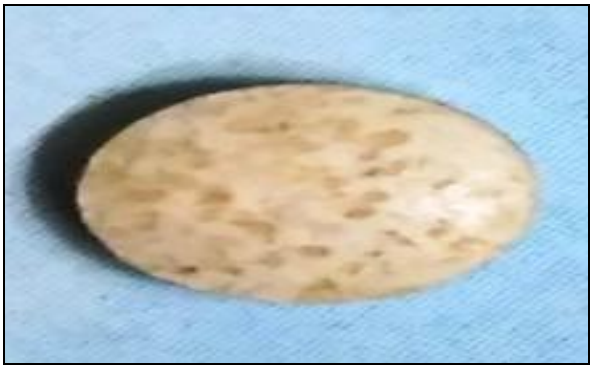

FIG. 2: ENTERIC COATED PECTIN BASED TABLET

Characterization of Dexamethasone Tablets:

Uniformity of Weight: For determining the uniformity of weight, twenty tablets were weighed individually and collectively. The weight variation was calculated [25]. The same procedure was used for coated tablet. The results are described in **Table 7-8.**

Hardness: The hardness of core tablet was determined by Monsanto Hardness Tester[26]. The results are presented in **Table 7-8.**

Friability: The friability of the core tablet was determined by Roche fribilator [27]. The values are presented in **Table 7-8.**

Thickness: The thickness of the tablet was determined by screw gauge [28]. The determination of thickness was carried out after each coating. The results are presented in **Table 7-8.**

Diameter: The diameter of the core tablet was determined with the help of Vernier Caliper [29]. The results are described in **Table 7-8.**

Drug Content: The uniformity of drug content in each formulation was determined by triturating 20 tablets, and powder equivalent to average weight was added to 100 ml of 5.0 pH PBS followed by stirring for 30 min.

The solution was filtered through Whattman filter paper, diluted suitably, and absorbance of the resultant solution was measured using double beam UV spectrophotometer 1700 E at λ_{max} 242. The results are shown in **Table 7-8.**

Drug content = Actual drug content / Theoretical drug content × 100

TABLE 7: PHYSICO-CHEMICAL CHARACTERIZATION OF OPTIMIZED CHITOSAN BASED TABLETS

S. no.	Formulation Code	Uniformity of Weight (in mg)	Thickness (in mm)	Drug Content (%)
1	F4S2E1	134.778±0.672	2.82±0.05	99.02±0.03
2	F4S2E2	136.068±0.864	2.80±0.08	98.23±0.04
3	F4S2E3	135.921±0.946	2.83±0.05	98.05±0.07

TABLE 8: PHYSICO-CHEMICAL CHARACTERIZATION OF OPTIMIZED PECTIN BASED TABLETS

S. no.	Formulation Code	Uniformity of Weight (in mg)	Thickness (in mm)	Drug Content (%)
1	P4M2C1	134.778±0.672	2.82±0.05	99.02±0.03
2	P4M2C2	136.068±0.864	2.80±0.08	98.23±0.04
3	P4M2C3	135.921±0.946	2.83±0.05	98.05±0.07

***In-vitro* Dissolution:** *In-vitro* dissolution studies for the optimized formulation of both chitosan and pectin-based tablets were carried out in USP XXV dissolution test apparatus (basket method) (Electolab TDL-08L). The tablets were tested for drug release for 2 h in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with phosphate buffer pH 6.8(900 ml) and tested for drug release for 2 h. Then the dissolution medium was further replaced with 100 ml phosphate buffer pH 7.4 with pectinase contained in 200-ml beaker, and immersed in water maintained in 900 ml vessel, which in turn was in the water bath of the apparatus [29]. 5 ml samples were withdrawn at predetermined time intervals for period 18 hr and replaced with the equal volume of the same dissolution medium. The samples were filtered, and the concentration of the drug was obtained by measuring the absorbance at 242 nm using a double beam UV-spectrophotometer (1700-E, Shimadzu). The content of the drug was calculated using the equation generated from the calibration curve. The test was performed in triplicate [29]. As shown in **Table 9-10** and **Fig. 3-4.**

TABLE 9: CUMULATIVE % DRUG RELEASE FROM VARIOUS OPTIMIZED CHITOSAN BASED TABLETS

S. no.	Time (h)	Cumulative % Drug Release from Various Formulations		
		F4S2E1	F4S2E2	F4S2E3
1	1	-	-	-
2	2	-	-	-
3	4	-	-	-
4	6	5.832±0.28	6.231±0.05	7.107±2.76
5	8	10.996±0.73	7.193±0.07	11.951±2.79
6	10	21.158±0.73	13.950±0.28	23.253±2.71
7	12	32.537±0.54	33.235±0.27	29.866±4.76
8	14	41.794±0.28	60.690±0.48	38.139±2.78
9	16	55.129±0.28	67.194±0.28	44.895±0.05
10	18	63.488±0.56	72.960±0.49	51.716±2.72
11	20	75.594±0.29	83.244±0.84	74.556±2.31
12	22	85.901±0.29	86.604±1.52	83.259±5.56
13	24	99.027±0.47	93.456±0.47	92.840±2.42

TABLE 10: CUMULATIVE % DRUG RELEASE FROM VARIOUS OPTIMIZED PECTIN BASED TABLETS

S. no.	Time (h)	Cumulative % Drug Release from Various Formulations		
		P4M2C1	P4M2C2	P4M2C3
1	1	-	-	-
2	2	-	-	-
3	4	-	-	-
4	6	5.832±0.28	6.231±0.05	7.107±2.76
5	8	10.996±0.73	7.193±0.07	11.951±2.79
6	10	21.158±0.73	13.950±0.28	23.253±2.71
7	12	32.537±0.54	33.235±0.27	29.866±4.76
8	14	41.794±0.28	60.690±0.48	38.139±2.78
9	16	55.129±0.28	67.194±0.28	44.895±0.05
10.	18	63.488±0.56	72.960±0.49	51.716±2.72
11.	20	75.594±0.29	83.244±0.84	74.556±2.31
12	22	85.901±0.29	86.604±1.52	83.259±5.56
13	24	95.027±0.47	93.456±0.47	92.840±2.42

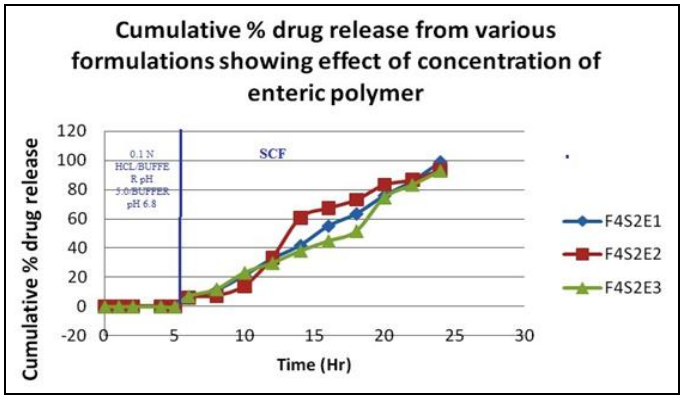

FIG. 3: EFFECT OF CONCENTRATION ENTERIC POLYMER ON DRUG RELEASE

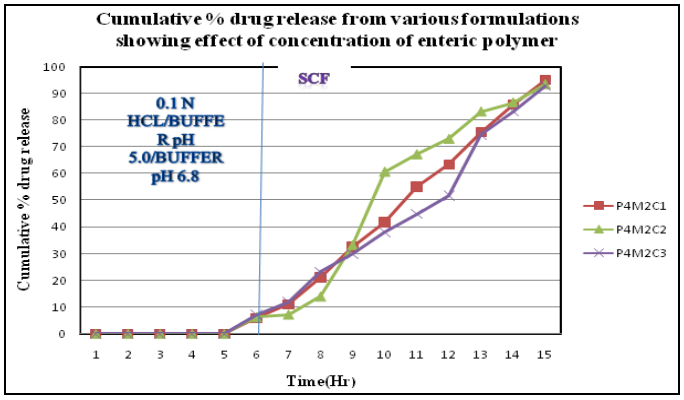

FIG. 4: EFFECT OF CONCENTRATION ENTERIC POLYMER ON DRUG RELEASE

Scanning Electron Microscopy Studies: In order to elucidate the mechanism of drug release from developed formulations, surface of coated tablets, both before and after dissolution studies, was studied for optimized formulation by using scanning electron microscope (SEM) (Leo-430, EDAX England) as shown **Fig. 5-8.**

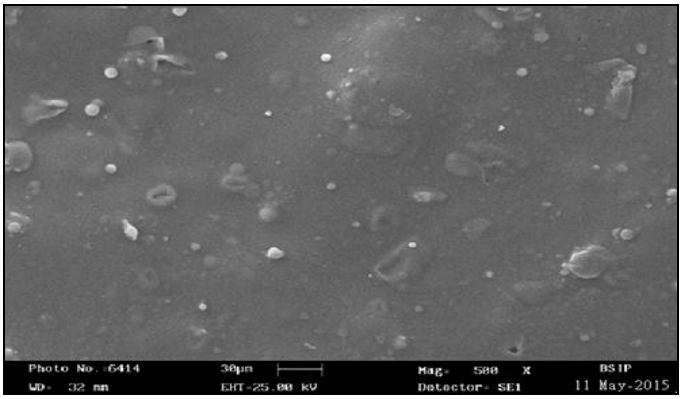

FIG. 5: SEM OF FORMULATION F4S2E1 BEFORE DISSOLUTION

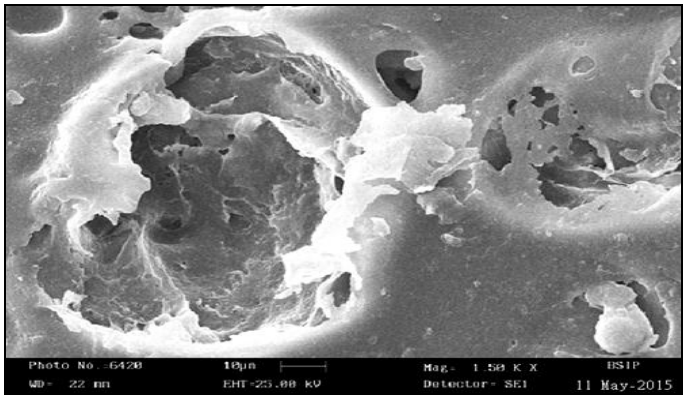

FIG. 6: SEM OF FORMULATION F4S2E1 AFTER DISSOLUTION

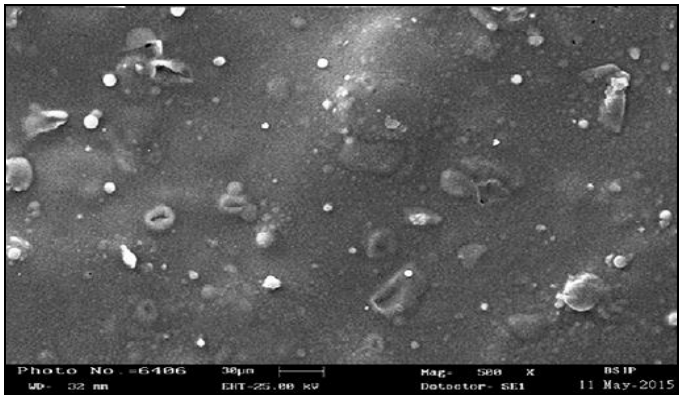

FIG. 7: SEM OF FORMULATION P4M2C1 BEFORE DISSOLUTION

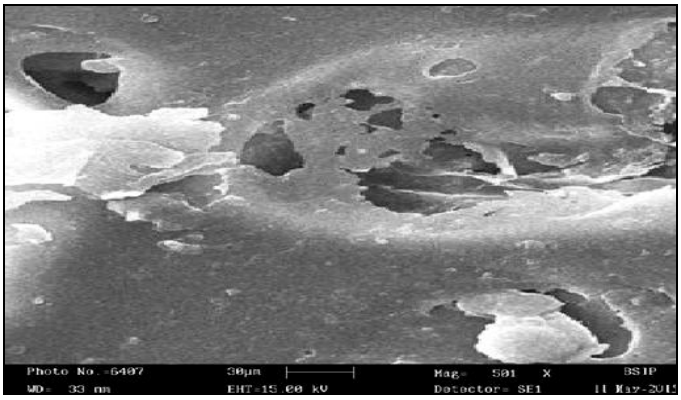

FIG. 8: SEM OF FORMULATION P4M2C1 AFTER DISSOLUTION

Accelerated Stability Studies: The accelerated stability study of optimized formulation (F4S2E1 & P4M2C1) was carried out.

The test was carried out by placing the tablets of each selected formula in a closed glass container in an ALU Blister pack and stored in thermostatically controlled ovens adjusted at different temperatures and humidity percentage, namely, 40 ºC/75%, 30 ºC/65%, and 25 ºC/ 60% for a period of 3 months. The results of the optimized formulations F4S2E1 after conducting accelerated stability studies for 3 months are as in **Table 11** to **14** and **Fig. 11-12.**

TABLE 11: STABILITY STUDY DATA FOR THE OPTIMIZED TABLET (F4S2E1)

S. no.	Test	Initial	Storage Condition						
			40 ºC /75% RH			30 ºC /60%RH			25 ºC /60% RH
			1 Month	2 Month	3 Month	1 Month	2 Month	3 Mmonth	3 Month
1	Av. weight	134.8	134.2	134.1	134	134.3	134.2	134.1	134
2	Hardness	8.52	8.7	8.76	8.8	8.52	8.7	8.76	8.8
3	LOD	2.50%	2.60%	2.60%	2.80%	2.50%	2.60%	2.70%	2.70%

TABLE 12: STABILITY STUDY (DISSOLUTION DATA) FOR THE OPTIMIZED TABLET BATCH (F4S2E1)

S. no.	Test	Initial	Storage Condition						
	Dissolution (h)		40^0C/75% RH			30^0C/60%RH			25^0C/60% RH
			1 Month	2 Month	3 Month	1 Month	2 Month	3 Month	3 Month
1	2	-	-	-	-	-	-	-	-
2	6	5.832±0.28	6.231±0.05	7.107±2.76	7.23±2.70	5.823±0.28	6.456±0.05	7.456±2.65	7.56±2.7
3	8	10.996±0.73	7.193±0.07	11.951±2.79	12.045±2.79	10.996±0.73	7.193±0.07	11.951±2.79	11.951±2.79
4	10	21.158±0.73	13.950±0.28	23.253±2.71	23.253±2.71	21.158±0.73	13.950±0.28	23.253±2.71	23.253±2.71
5	12	32.537±0.54	33.235±0.27	29.866±4.76	29.866±4.76	32.537±0.54	33.235±0.27	29.866±4.76	29.866±4.76
6	14	41.794±0.28	60.690±0.48	38.139±2.78	38.139±2.78	41.794±0.28	60.690±0.48	38.139±2.78	38.139±2.78
7	16	55.129±0.28	67.194±0.28	44.895±0.05	44.895±0.05	55.129±0.28	67.194±0.28	44.895±0.05	44.895±0.05
8	18	63.488±0.56	72.960±0.49	51.716±2.72	51.716±2.72	63.488±0.56	72.960±0.49	51.716±2.72	51.716±2.72
9	20	75.594±0.29	83.244±0.84	74.556±2.31	74.556±2.31	75.594±0.29	83.244±0.84	74.556±2.31	74.556±2.31
10	22	85.901±0.29	86.604±1.52	83.259±5.56	83.259±5.56	85.901±0.29	86.604±1.52	83.259±5.56	83.259±5.56
11	24	99.027±0.47	99.456±0.42	99.012±2.42	99.34±2.43	99.03±2.44	99.034±2.45	99.056±2.46	99.06±2.47

TABLE 13: STABILITY STUDY DATA FOR THE OPTIMIZED TABLET (P4M2C1)

S. no.	Test	Initial	Storage Condition						
			40^0C /75% RH			30^0C /60%RH			25^0C/60% RH
			1 Month	2 Month	3 Month	1 Month	2 Month	3 Month	3 Month
1	Av. weight	134.8	134.2	134.1	134	134.3	134.2	134.1	134
2	Hardness	8.02	8.04	8.07	8.1	8.02	8.06	8.1	8.1
3	LOD	2.50%	2.50%	2.60%	2.60%	2.80%	2.50%	2.60%	2.70%

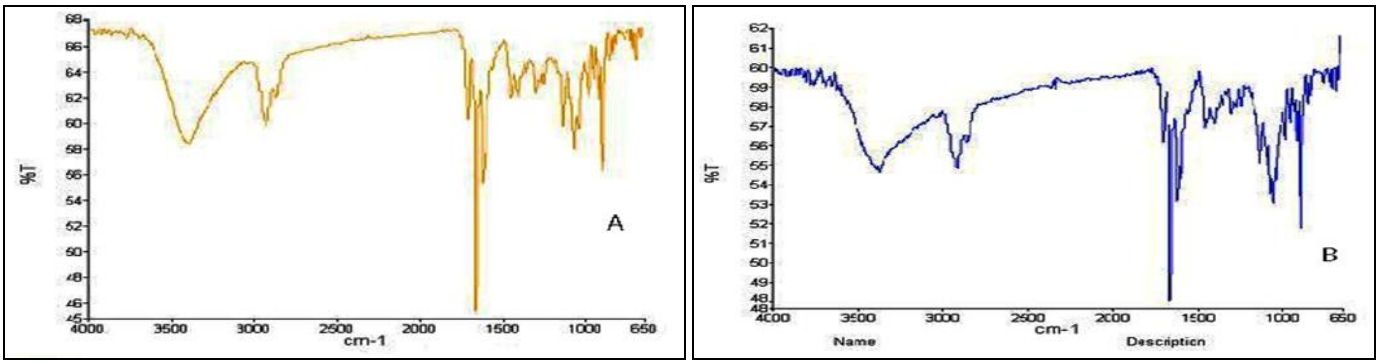

FIG. 11: FTIR SPECTRA OF F4S2E1 AFTER 3 MONTHS OF EXPOSURE AT 40 ºC AND 75% RELATIVE HUMIDITY

TABLE 14: STABILITY STUDY (DISSOLUTION DATA) FOR THE OPTIMIZED TABLET BATCH (P4M2C1)

S. no.	Test	Initial	Storage Condition						
1	Dissolution (h)		40^0C/75% RH			30^0C/60%RH			25^0C/60% RH
2			1 Month	2 Month	3 Month	1 Month	2 Month	3 Month	3 Month
3	2								
4	6	5.832±0.28	6.231±0.05	7.107±2.76	7.23±2.70	5.823±0.28	6.456±0.05	7.456±2.65	7.56±2.7
5	8	10.996±0.73	7.193±0.07	11.951±2.79	12.045±2.79	10.996±0.73	7.193±0.07	11.951±2.79	11.951±2.79
6	10	21.158±0.73	13.950±0.28	23.253±2.71	23.253±2.71	21.158±0.73	13.950±0.28	23.253±2.71	23.253±2.71
7	12	32.537±0.54	33.235±0.27	29.866±4.76	29.866±4.76	32.537±0.54	33.235±0.27	29.866±4.76	29.866±4.76
8	14	41.794±0.	60.690±0.	38.139±2.	38.139±2.	41.794±0.	60.690±0.	38.139±2.	38.139±2.78

		28	48	78	78	28	48	78	
9	16	55.129±0.	67.194±0.	44.895±0.	44.895±0.	55.129±0.	67.194±0.	44.895±0.	44.895±0.05
		28	28	05	05	28	28	05	
10	18	63.488±0.	72.960±0.	51.716±2.	51.716±2.	63.488±0.	72.960±0.	51.716±2.	51.716±2.72
		56	49	72	72	56	49	72	
11	20	75.594±0.	83.244±0.	74.556±2.	74.556±2.	75.594±0.	83.244±0.	74.556±2.	74.556±2.31
		29	84	31	31	29	84	31	
12	22	85.901±0.	86.604±1.	83.259±5.	83.259±5.	85.901±0.	86.604±1.	83.259±5.	83.259±5.56
		29	52	56	56	29	52	56	
13	24	95.027±0.	95.012±0.	95.01±2.4	95.01±2.4	95.023±0.	95.012±0.	95.01±2.4	95.023±2.42
		47	47	2	2	47	47	2	

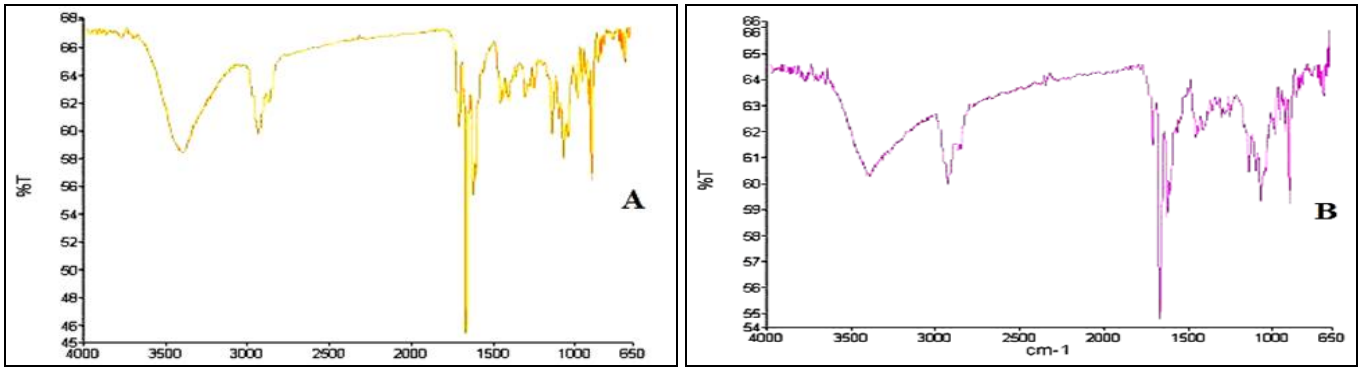

FIG. 12: FTIR SPECTRA OF P4M2C1 AFTER 3 MONTHS OF EXPOSURE AT 40 ºC AND 75% RELATIVE HUMIDITY

RESULTS AND DISCUSSION: The microbially triggered systems of dexamethasone based on chitosan and Pectin for colonic targeted drug delivery are formulated. The tablets are formulated by a direct compression method followed by enteric coating. Then tablets are evaluated for various parameters.

The formulation code F4S2E1 in the case of chitosan and P4M2C1 in the case of pectin shows the best results. The % drug content in F4S2E1 and P4M2C1 was found 99.02±0.03 and 98.68±0.04, respectively. The cumulative % drug release study showed that maximum drug release was found in the case of F4S2E1 and P4M2C1 was 99.027±0.47 and 95.027±0.47 respectively at 24 h.

The *in-vitro* release shows that the drug as almost completely (99.247±0.54) released in SCF after 24 h. It also be seen that there was no significant variation in the physical appearance, average weight, hardness, and loss of drying after stability study for a period of 3 months. From the results, it also had been concluded that drug-containing chitosan polymer shows best results than pectin polymers, and Thus Colon targeted drug delivery was achieved by using a chitosan-based osmotic tablet with complex film and a multilayer coating system. These findings are extremely important from a commercial point of view as the prepared formulation removes the drawback of degradation and poor dissolution profile of dexamethasone and improves its effect.

CONCLUSION: In the study new microbially triggered system based on chitosan and pectin for colonic targeted drug delivery is formulated. The results from various evaluations show that formulation code F4S2E1 and P4M2C1 are found to be optimized batch. In both formulations, F4S2E1 shows better results in all parameters. The drug was almost completely released in SCF after 24 h. The basic mechanism of colon-targeted osmotic pump formulation was based on the gellable property at acid conditions and colon-specific biodegradation of polymers. The SEM indicated that both polymers were accessible to enzymatic degradation, which allowed the in situ formation of delivery pores for releasing drugs under conditions that may be expected in the colon for a long time. Thus the developed system was found to be a potential system for targeting and controlling the release of drug to the colon achieved by using chitosan and pectin based osmotic tablet.

ACKNOWLEDGEMENT: The authors thank Mrs. Anjali Kushwaha, Associate Professor, Kanpur Institute of technology and Pharmacy, for

assistance in writing skills and also help in formatting the manuscript, respectively.

CONFLICTS OF INTEREST: The authors confirm that this article's content has no conflict of interest.

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How to cite this article:
Gupta R, Agarwal A and Kushwaha A: To study the effect of natural polymer on the release of osmotic tablet for colon specific drug delivery sysyem. Int J Pharm Sci & Res 2021; 12(6): 3410-17. doi: 10.13040/IJPSR.0975-8232.12(6).3410-17.