International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 5, 2022

Original Article

FORMULATION OF MESALAMINE-LOADED RECTAL MUCOADHESIVE PELLETS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE USING 3^2FULL FACTORIAL DESIGN

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Received: 12 May 2022, Revised and Accepted: 15 Jun 2022

ABSTRACT

Objective: The objective of the present work was to optimize a rectal suppository containing mucoadhesive pellets of Mesalamine to achieve local yet sustained release of Mesalamine for once-a-day administration for the therapy of Inflammatory Bowel Disease.

Methods: Thus, the present work involves forming mucoadhesive pellets of mesalamine by extrusion spheronization, which were then loaded into a suppository to be administered rectally. The pellets were evaluated for mucoadhesion strength, swelling potential, morphology, particle size, drug release, drug loading and retention time.

Results: The optimized batch of pellets using Eudragit RLPO as the release retardant, carrageenan as a mucoadhesive polymer and other excipients had a mucoadhesion strength of 0.143 N, a swelling index of 50.50 %, and 44 % and 75 % drug was released from them at the end of 6 and 15 h respectively. The pellets-loaded cocoa butter suppositories had a melting range of 35–37 °C, disintegrated within 8–9 min and had a hardness of 4–5 kg/cm^3. A comparison of the *in vitro* drug release profile from the mucoadhesive pellets and the mucoadhesive pellets-loaded suppositories showed a closeness in the % cumulative drug release indicating that cocoa butter did not interfere in the release of the drug from the pellets.

Conclusion: Mucoadhesive Pellets were successfully developed by extrusion spheronizer technique and incorporated into suppositories. *In vitro* study revealed a release profile that warranted a once-a-day regimen leading to a reduction in the requirement of the drug and hence the side effects.

Keywords: Inflammatory bowel disease, Extrusion, Spheronization, Suppository, Sustained release, Mucoadhesion

DOI: https://dx.doi.org/10.22159/ijap.2022v14i5.45180. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Inflammatory Bowel Disease (IBD) are various chronic and relapsing inflammatory conditions in which the body's immunity framework assaults the parts of the digestive system [1]. IBD is partitioned into two conditions, Crohn's disease (CD) and ulcerative colitis (UC), which are impacted by ongoing inflammation of the gastrointestinal tract (GIT) [2]. There is no absolute remedy for IBD; exceptions to that are the medicines responsible for lessening and controlling the indications of the disease. In CD, irritation can happen in any segment of the GIT, yet it most often influences the terminal section of the small intestine and the initial length of the large intestine. In the case of UC, aggravation primarily occurs in the innermost lining of the colon and the rectum. The exact cause of IBD is obscure; however, IBD is the consequence of an imperfect immune system. An appropriately working immune system assaults unfamiliar organic entities, for example, infections and microorganisms, to secure the body. However, on account of IBD, the immune system botches innocuous substances in the digestive system as foreign and dispatches an assault, bringing about inflammation. A mix of four elements is purported to cause IBD, viz, hereditary elements like enhanced intestinal permeability, natural factors, an irregularity of GI microflora, and an improper response from the immunity apparatus [3]. Manifestations of IBD are fever, loss of hunger, weight reduction, sluggishness, late evening perspiring, development impediment and amenorrhea [4].

Mesalamine (MSL) is the first-line choice in the treatment of mild-to-moderate UC [5, 6]. It has multiple anti-inflammatory actions that include inhibiting leukotrienes and Interleukin-1 production, lessening mucosal inflammation by acting on mucosal colonic epithelial cells, and acting as a free radical scavenger [7]. Although effective orally, the treatment is plagued by serious adverse reactions such as allergic reactions, pancreatitis, hepatotoxicity, bone marrow suppression, interstitial nephritis, and haemolytic anemia or megaloblastic anemia. All of these could be attributed to the systemic absorption and the non-specific distribution of the drug [8]. Thereby there is a need to find an alternative to the oral administration of MSL. One such solution could be the rectal delivery of the drug under consideration. This would provide benefits like targeted action, a quicker response time and a reduction in the frequency of dosing. Studies have suggested that topical preparations result in better responses and a quicker improvement in the case of mild-to-moderate distal UC when compared with oral therapy. The rectal delivery of 5–aminosalicylic acid led to its mucosal concentration being 200-fold higher than that could be achieved by oral administration alone [9].

Rectal preparations range from conventional enemas and suppositories to novel formulations like sustained release multiparticulates that could be incorporated into the conventional forms to reap the benefits of both the traditional and modern formulations. Multiparticulates are the discrete, small and repetitive units of drug particles that may or may not possess similar drug release profiles. They could be programmed to provide a delayed, controlled or pulsatile drug release pattern. They have a distinct benefit, owing to their small size, generally less than 200 µm, they are not affected by the variations in the gastric and intestinal transit time and would reach the target site, i.e., the colon, quickly [10]. On account of the same consideration, they would house in the ascending colon for a longer period as compared to a large, single unit dosage form. The success of the therapy depends not only on the swiftness with which the drug reaches the intended target site but also on the duration for which it resides in the said location. One such account of increasing the residence time of any formulation is the incorporation of mucoadhesive polymers, which would prolong the time for which the dosage form stays in the colon [11]. A lot of research is being focussed on using natural polymers for formulation development due to their natural biodegradability, thus, carrageenan would be used as the polymer to formulate mucoadhesive pellets [12].

Thus, the objective of the present work was to optimize a rectal suppository containing mucoadhesive pellets of MSL to achieve local

yet sustained release of MSL for once-a-day administration for the therapy of IBD.

MATERIALS AND METHODS

Materials

Mesalamine was received as a gift sample from Zydus Research Centre. (Ahmedabad, India), microcrystalline cellulose (MCC) was purchased from SD Fine Chem Ltd. (Mumbai, India), carrageenan was acquired from Angel Pharma India Pvt. Ltd. (Rajkot, India), Eudragit RLPO was obtained from Vikram Thermo Ltd. (Ahmedabad, India), polyvinyl pyrrolidone (PVP) K30 and glycerine were bought from Molychem (Mumbai, India), isopropyl alcohol was secured from Loba Chemie Pvt. Ltd. (Mumbai, India), and cocoa butter base was procured from Chemdyes Corporation (Rajkot, India).

Preparation of mucoadhesive pellets

The mucoadhesive pellets were prepared by the process of extrusion spheronization [13, 14]. The drug, along with the mucoadhesive polymer carrageenan and the enteric-responsive polymer Eudragit RLPO was mixed with glycerine and a damp mass was formed using a 10 % w/v solution of PVP K30 in isopropanol. A chrominac extruder was employed to extrude the damp mass. The extrudes were then converted into spherical pellets by using a spheronizer. The pellets so obtained were then dried at 35 °C in a hot air oven for 30 min. The dried pellets were then screened to get a uniform particle size distribution.

Optimization of mucoadhesive pellets

To optimize the formulation and process variables, the two critical parameters were noted that could have a significant impact on the physicochemical and the performance characteristics of the prepared pellets. They were the amount of Eudragit RLPO and the operational speed of the spheronizer. These were then optimized using a full 3^2 factorial design. Nine trials were conducted as per the design generated using Design Expert® 6.8 as listed in table 1. The optimization of the amount of the polymer Eudragit RLPO (X_1) was carried out between the range of 0.7 to 1.3 g and the operational speed of the spheronizer (X_2) was scanned in the range of 2000 to 2400 rpm. The mucoadhesive strength (Y_1), the swelling index (%) (Y_2), and cumulative drug release (CDR) (%) at the end of 6 (Y_3) and 15 h (Y_4) were fixed as the dependent variables for the study. The analysis of variance (ANOVA) was performed to decide the right model fit. The equations for all the dependent variables were obtained. The response surface plots were generated to understand the effect of interactions of the respective dependent variable. An overlay plot was constructed to narrow down the region of the independent variables that would lead to the development of a robust product with the desired properties, viz., a high mucoadhesive strength (>0.13 N), % swelling of 40–50 % w/w, a % CDR of 40–50 at the end of 6 h and that of >70 % at the end of 15 h. Along with these, the effect of the two independent variables was also studied on the particle size and the residence time of the pellets.

Table 1: Details of batches taken as per the 3^2 full factorial study design

Batch number	Quantity of ingredient (g)				Volume of ingredient (mL)		Spheronizer speed (rpm)
	MSL	MCC	Carrageenan	Eudragit RLPO	PVP K30 in isopropanol (10 % w/v)	Glycerine	
F1	3.0	0.4	1.4	0.7	3.0	1	2000
F2	3.0	0.4	1.4	0.7	3.0	1	2200
F3	3.0	0.4	1.4	0.7	3.0	1	2400
F4	3.0	0.4	1.4	1.0	3.0	1	2000
F5	3.0	0.4	1.4	1.0	3.0	1	2200
F6	3.0	0.4	1.4	1.0	3.0	1	2400
F7	3.0	0.4	1.4	1.3	3.0	1	2000
F8	3.0	0.4	1.4	1.3	3.0	1	2200
F9	3.0	0.4	1.4	1.3	3.0	1	2400

Evaluation of mucoadhesive pellets

Ex vivo mucoadhesion strength test

The *ex vivo* mucoadhesion strength test was performed on freshly cut goat mucosa [15]. The goat mucosa was tied on the glass slide (28 mm 96 mm), and a pre-weighed quantity of mucoadhesive pellets previously hydrated with phosphate buffer pH 7.4 was adhered to the mucosa by applying light force for 30 seconds. The modified physical balance was adjusted by keeping the glass beaker on another side. Water was added by burette and the weight of water needed to disengage the pellets from the exterior of goat mucosa was recorded for the measurement of mucoadhesive strength in grams. The force of adhesion in Newton (N) was quantified by using equation 1.

$$\text{Force of Adhesion (N)} = \frac{\text{Mucoadhesive strength (g)}}{1000} \text{ X } 9.81\text{----1}$$

Swelling index (% w/w)

The ability of the prepared mucoadhesive pellets to swell in pH 7.4 phosphate buffer was determined by permitting them to swell up to their steadiness. Weighed pellets (W_1) were added to a beaker containing 5 ml of the buffer medium at 37 °C. After 24 h, swollen pellets were extracted from the medium, blotted to dryness, and weighed (W_2). The swelling index was computed using equation 2 [16, 17].

$$\text{Swelling index (\%)} = \frac{W_2 - W_1}{W_1} \text{ X } 100\text{----------2}$$

In vitro drug release

The *in vitro* drug release of the mucoadhesive pellets was investigated using the USP 43 dissolution apparatus I (basket apparatus). The medium used was phosphate buffer of pH 7.4 (900 ml) maintained at 37±0.5 °C. Pellets equivalent to 800 mg MSL were used to perform the study. The aliquotes (5 ml) were taken out at preset times and replaced by the fresh buffer. The test was run for a total duration of 15 h. The samples were filtered, diluted and analyzed spectrophotometrically at 232 nm [18, 19].

Ex vivo residence time

The *ex vivo* residence time was studied using a locally modified USP paddle apparatus. The medium (phosphate buffer pH 7.4) was maintained at 37 °C. A piece of goat intestine was cemented to the surface of a glass slab which was then anchored upright to the paddle. The mucoadhesive pellets were hydrated on one side using the media and then the damp surface was brought in proximity to the mucosal film. The paddle was rotated at a gentle speed of 50 rpm. The time required for the complete freeing of the pellets from the mucosal facet was recorded [20]. The experiment was performed in triplicate and the results were expressed as mean±standard deviation (SD).

Particle size

Pellets were dispersed in liquid paraffin, mounted on a clean glass slide, and placed on the mechanical stage of the microscope. An ocular micrometer fitted with the microscope was pre-calibrated with the use of a stage micrometer at less than 10 × 45 magnification. The diameter of 150 particles was noted using a calibrated stage micrometer. From the data, the average particle size was calculated, and the results were expressed as mean±standard deviation (SD).

Drug loading

Dried pellets were triturated and 250 mg of the powder was dissolved in 250 ml of 0.1 N hydrochloric acid. After filtration and suitable

dilution, the absorbance was noted spectrophotometrically at 232 nm. The concentration was calculated using the standard curve method.

Morphological investigation

Scanning Electron Microscopy (SEM) was used to determine the sphericity and the shape of pellets [21]. The sample was fixed on an aluminium stub with conductive double-sided fixative tape and glazed with gold in an argon atmosphere (50 Pa) at 50 mA for 50 s. The samples were scrutinized at a voltage of 5 kV. The specimens were surveyed directly in SEM using Smart SEM TM software (Carl Zeiss, EVO18, UK) at Agriculture University, Junagadh, Gujarat.

Fabrication of mucoadhesive pellets-loaded suppositories

The pour moulding technique of preparing suppositories was employed for the preparation of the suppositories. The cocoa butter base was melted at 35 °C and the pellets equivalent to a single dose of MSL were dispersed in the molten base. The mixture was continuously stirred and poured in pre-lubricated moulds having a capacity of 3.5 ml. The blend was allowed to congeal gradually and then suppositories were collected post-complete solidification.

Evaluation of mucoadhesive pellets-loaded suppositories

Melting range

The prepared suppositories were evaluated for the macro and micro melting ranges. The macro melting range was determined by measuring the time taken for the entire suppository to melt when immersed in a constant temperature bath maintained at 37±0.5 ˚C. Micro melting range test was carried out by using a capillary tube of 10 cm length in which the formulation was filled up to 1 cm height and dipped in the water bath. The temperature was increased slowly and the one at which the mass liquefies was noted [22].

Softening point

A pipette having a narrow opening on one side and a broad opening on another side was used to determine the softening time of the suppositories. The pipette was dipped in hot water maintained at 37 ˚C. So, that the tapered end faces the hot water. The suppository was introduced through the broad end at the top of the pipette and gently pushed down its expanse until it reaches the end. A glass rod was then thrust into it so that it rests just over the suppository. The temperature at which the rod just dipped down was noted, this represents the liquefaction temperature and the time at which the glass rod reaches the end after the complete melting of suppositories is the softening time [23].

Weight variation

Twenty suppositories were weighed, and the average weight was calculated. The suppositories were then individually weighed. Not more than two suppositories out of the 20 samples taken may deviate from the average by more than 5% and none deviate more than 10 % from the average weight [24, 25].

Disintegration time

The disintegration time of the suppositories was determined by using the USP disintegration test apparatus. The time taken for the disintegration of the entire suppository was recorded. Phosphate buffer pH 7.4 maintained at 37±0.5 °C was employed as the medium for this test [26].

Hardness test

The hardness test is carried out to determine the tensile strength of the suppositories. The hardness of the formulated suppositories was tested using the Monsanto hardness tester [27]. The experiment was performed in triplicate and the results were expressed as mean±standard deviation (SD).

***In vitro* drug release**

The *in vitro* drug release of the mucoadhesive pellets was investigated using the USP 43 dissolution apparatus I (basket apparatus). The medium used was phosphate buffer of pH 7.4 (900 ml) maintained at 37±0.5 °C.

The suppository was placed in the metal basket which was rotated at 50 rpm. 2 ml of the aliquot was withdrawn every 10 min, filtered and analyzed using a UV spectrophotometer at 330 nm. The studies were continued for 15 h [28].

RESULTS

Optimization of mucoadhesive pellets

The results of the optimization studies were reported in table 2. The drug release profile of all the batches were as depicted in fig. 1. The ANOVA was performed, and the model was fitted for each dependent variable. The equations were constructed for each dependent variable as listed in table 3.

Table 2: Results of the trials taken during the optimization studies

Batch number	Mucoadhesive strength (N) (Y_1)	% Swelling Index (Y_2)	% CDR at 6 h (Y_3)	% CDR at 15 h (Y_4)	Particle size (µm)	Residence time (h)
F1	0.143±0.001	50.50±0.3	43.45	73.36	678.3±52.2	15.00±0.015
F2	0.140±0.0005	48.20±0.01	43.35	73.26	632.2±67.3	15.00±0.097
F3	0.137±0.0005	50.00±0.00	43.23	73.12	596.5±86.7	14.04±0.14
F4	0.119±0.001	43.40±0.04	41.68	72.36	671.5±56.3	13.5±0.764
F5	0.115±0.0005	44.30±0.00	41.52	71.42	627.7±68.1	13.2±0.951
F6	0.117±0.001	45.80±0.3	41.38	71.03	594.1±85.2	13.7±0.115
F7	0.103±0.0005	35.30±0.02	39.89	69.62	676.9±65.2	12.2±0.090
F8	0.104±0.0005	36.20±0.04	39.74	69.51	633.9±69.4	12.6±0.466
F9	0.103±0.0005	37.80±0.01	39.58	69.32	601.3±76.1	12.5±0.868

*±Values indicate the triplicate trials (n=3)

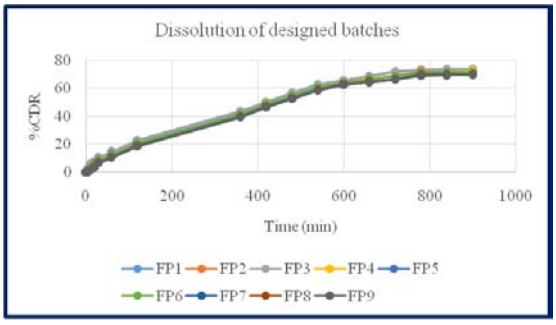

Fig. 1: *In vitro* drug release profile of the batches taken during optimization

Table 3: Polynomial equations generated for dependent variables

Dependent variable	Polynomial equation	Predicted R^2
Mucoadhesive Strength (N) (Y_1)	$0.1167+0.0005\ X_1-0.0182\ X_2-0.0013\ X_{12}+0.0005\ X_{11}+0.0045\ X_{22}$	0.9936
% Swelling Index (Y_2)	$43.90+0.7333\ X_1-6.57\ X_2+0.90\ X_{12}-1.50\ X_{11}+0.75\ X_{22}$	0.9927
% CDR at 6 h (Y_3)	$34.85-0.7367\ X_1-5.59\ X_2+0.4400\ X_{12}+0.1433\ X_{11}-2.95\ X_{22}$	0.9971
% CDR at 15 h (Y_4)	$85.41-1.48\ X_1-4.91\ X_2+0.8375\ X_{12}+3683\ X_{11}-0.1867\ X_{22}$	0.9867

The 3D response surface plots to study the interaction between the independent variable affecting the dependent variables were plotted and were as shown in fig. 2. The overlay plot constructed for the selection of the independent variables to get mucoadhesive pellets with the desired characteristics was as shown in fig. 3.

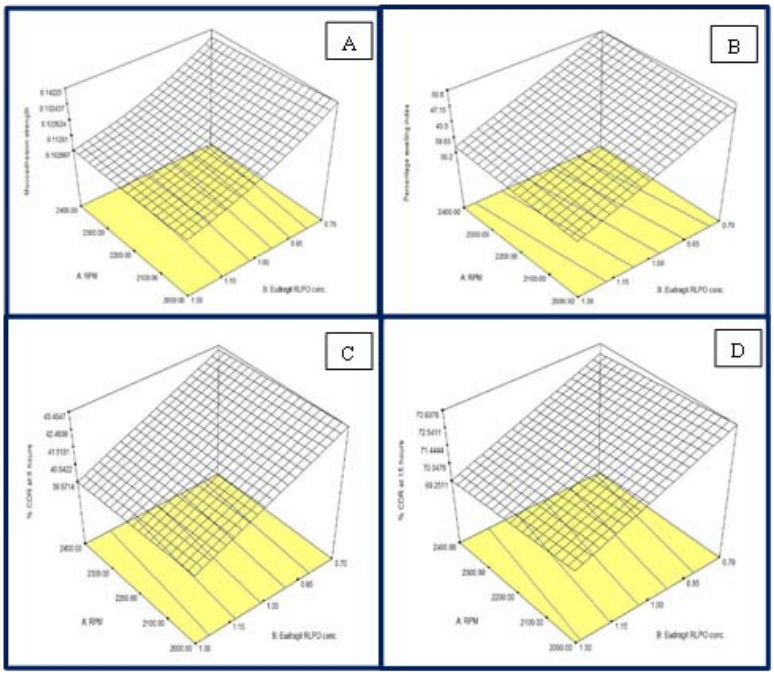

Fig. 2: 3D Response surface plots for (A) Mucoadhesive strength, (B) % Swelling index, (C) % CDR at 6 h, and (D) % CDR at 15 h

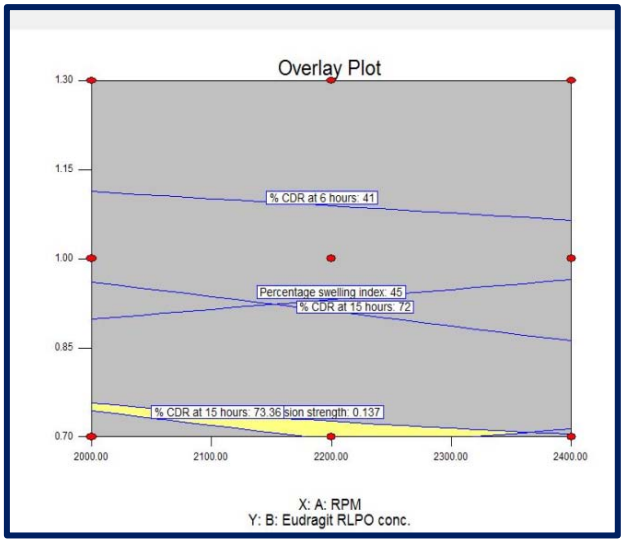

Fig. 3: Overlay plot for the selection of the optimized batch

The optimization trials gave a selection of combinations of the independent variables to yield pellets with the desired features. To confirm the validity of the results obtained, the selected batch was scaled up and the results were compared by calculating the % bias between the predicted and the experimental batch using equation 3. The expected % bias should be below 10%. The values so obtained are given in table 4.

$$\text{Bias (\%)} = \frac{\text{Predicted value} - \text{Experimental value}}{\text{Experimental value}} \text{X100----------3}$$

Table 4: Predicted and experimental values of the dependent variables

Dependent variable	Experimental value	Predicted value	% Bias
Mucoadhesive Strength (N) (Y_1)	0.143	0.137	0.003
% Swelling Index (Y_2)	50.50	45.00	5.5
% CDR at 6 h (Y_3)	44.45	41.00	3.45
% CDR at 15 h (Y_4)	75.26	72.00	3.26

Drug loading

The drug loading of all the batches ranged from 88.66 to 95.02 %. The drug loading of the optimized batch was found to be 96.13±2.15 %. This was used to calculate the equivalent weight of the pellets for the final formulation.

Morphological investigation

The result of the SEM analysis is shown in fig. 4. SEM scans confirmed the sphericity of the prepared pellets.

Evaluation of mucoadhesive pellets-loaded suppositories

The results of the physicochemical evaluation of the mucoadhesive pellets-loaded suppositories are listed in table 5 and the *in vitro* drug release profile from the suppositories is shown in fig. 5.

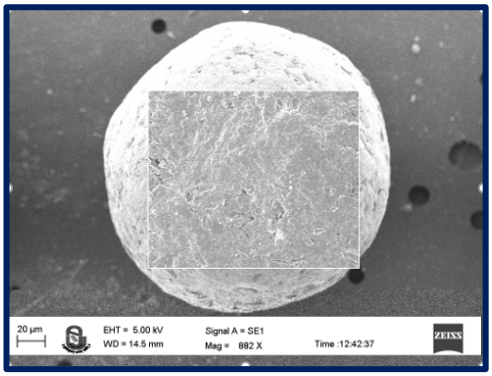

Fig. 4: SEM scan of the mucoadhesive pellet

Table 5: Results of evaluation of mucoadhesive pellets-loaded suppositories

Melting range (°C)		Softening point		Weight variation (g)	Disintegration time (min)	Hardness (Kg/Cm³)
Macro	Micro	Time (min)	Temperature (°C)			
36.8±0.4	35.7±0.7	2.89±0.03	37±0.8	2.89±0.03	8.6±1.5	4.35±0.65

*±Values indicate the triplicate trials (n=3)

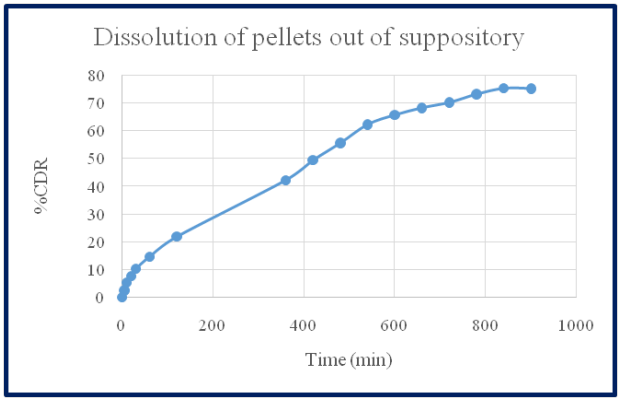

Fig. 5: *In vitro* drug release profile from the mucoadhesive pellets-loaded suppository

DISCUSSION

The selection of Independent variables were done after performing preliminary trials. Preliminary trials showed that Spheronizer speed(RPM) affects pellets size and Eudragit RLPO Concentration (gm) affects drug release as well as mucoadhesive strength, % Swelling Index from a formulation. Similar variables have been chosen by other researchers to optimize pellets prepared by extrusion sphernization, like Muley and co-workers have identified spheronizer speed and duration as key factors affeting the quality of the pellets obtained [29]. Veerubhotla and Walker had identified concentrations of the polymer, Eudagit RL 30D and sphernizer speed to be critical parameters affecting the performance of pellets [30]. So, based on these observations and literature review select two independent variables,X_1= Spheronizer speed (RPM) and X_2= Eudragit RLPO Concentration (gm). From the results of the optimization trials it could be concluded that the impact of the increase in the amount of the polymer, Eudragit RLPO was not conducive to the mucoadhesion strength of the pellets. This could be attributed to the reduced exposure of the mucoadhesive polymer, carrageenan to the environment and thereby reducing the strength of the bonds formed. As expected, the swelling index was found to be dependent solely on the amount of polymer, Eudragit RLPO present in the batch. An inverse relationship was observed between the two indicating that the presence of Eudragit RLPO would lessen the swelling of the pellets, which would, in turn, affect the mucoadhesive strength as well as the drug release from the pellets as seen from the results in table 2. Similar observations were made by Scientist Ruiz and Ghaly while they were formulating a bilayered mucoadhesive tablet of chlorpheniramine maleate [31]. The % CDR from the pellets were affected by the amount of Eudragit RLPO, which showed an inverse proportionality on the drug release. The study proved that Eudragit RLPO was capable of retarding the drug release and thereby prolonging the drug action at the target site. A similar result was observed by Gandhi *et al.*, who prepared nanoparticles of acyclovir using Eudragit RLPO and reported a drug release profile

spanning 24 h [32]. This proves that the combination of a hydrophobic polymer such as Eudragit RLPO and a water-swellable one like carageenan can help to modulate the rate of drug release to get a controlled release pattern. Eudragit RLPO was employed to retard the rate at which the fluid penetrated into the formulation matrix. A similar observation was made by Mehta and coworkers who used hyrophobic polymers like Eudragit RLPO and RSPO to produce a slow-release naproxen matric tablet for targeted colon drug delivery [33].

The spheronizer speed had an inverted correlation with the particle size. As expected, the particle size decreased as the spheronizer speed increased. This could be attributed to the hard environment faced by the pellets causing them to break into smaller sizes. A similar phenomenon has been reported by Srujan Kumar *et al.* and Wan *et al.* [34, 35]. The closeness in the predicted and the experimental values confirmed the validity of the results of the optimization trials.

Cocoa butter was selected as the base to prepare the suppositories as it is well tolerated by the rectal mucosa [36]. There are various polymorphic forms of cocoa butter out of which the β form is the most desired as it melts close to the body temperature, making it the ideal suppository base. The suppositories so formed were without any pits or fissures or any such visual defects. From the other parameters evaluated, it could be concluded that the method used gave suppositories that were relatively hard to allow for insertion without any undue discomfort to the patient yet could dissolve at body temperature within 10 min allowing for the release of the mucoadhesive pellets, which could then adhere to the mucosa and release the drug slowly over a prolonged period. A comparison of the *in vitro* drug release profile from the mucoadhesive pellets and the mucoadhesive pellets-loaded suppositories showed a closeness in terms of the % CDR indicating that cocoa butter did not interfere in the release of the drug from the pellets and that it could be used as a base to deliver the mucoadhesive pellets of MSL. Other researchers such as Saleem *et al.*, Reddy *et al.*, Bartels *et al.*, to name a few have made use of cocoa butter to effect the controlled release of various drugs [27, 37, 38].

CONCLUSION

It could be concluded from the present study that the mucoadhesive pellets-loaded suppositories could be made successfully by using cocoa butter as the base, carrageenan as the mucoadhesive polymer, and Eudragit RLPO as the enteric-responsive polymer to modulate the swelling and eventual drug release from the pellets. The *in vitro* drug release studies revealed a promising solution to target the mesalamine to the colon and thereby reduce the side effects associated with the non-specific distribution of the drug when given orally. Studies conducted so far revealed promising results, recommending an extension for additional pharmacokinetic assessment.

ACKNOWLEDGMENT

The authors would like to thank College for their kind support during the study and all other lab studies.

ABBREVIATIONS

IBD: Inflammatory Bowel Disease, CD: Crohn's Disease, UC: Ulcerative Colitis, GIT: Gastro-Intestinal Tract, MSL: Mesalamine, MCC: Microcrystalline Cellulose, PVP: Polyvinyl Pyrrolidone, CDR: Cumulative Drug Release, N: Newton, SD: Standard Deviation, SEM: Scanning Electron Microscopy, Mg: Milligram, G: Gram, Min: Minute, H: Hour, USP: United States Pharmacopoeia, ANOVA: Analysis of Variance

FUNDING

The authors did not have any financial assistance from any source, and it was self-funded research work.

AUTHORS CONTRIBUTIONS

The idea was conceptualized and the experimental design was fixed by both authors. Ms. Payal N. Vaja was responsible for conducting experiments, collecting data and analyzing it under the guidance of Dr. Chetan M. Detroja. The manuscript was prepared by Ms. Payal N. Vaja and critically reviewed by Dr. Chetan M. Detroja. The manuscript has been read and approved by both authors.

CONFLICTS OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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