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Formulation and Evaluation of Colon Targeted Suppository of Mesalazine

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ABSTRACT

The aim of the present investigation was to formulate and evaluate of Colon Targeted Suppository of Mesalazine. The attempts have been made to increase the dissolution of BCS class IV drug Mesalazine using Cocoa butter, Polyethylene Glycol 6000, Polyethylene Glycol 9000 as base which was prepared by Fusion Method. Base combinations was prepared. Total three formulations of each combinations of base (Cocoa butter: Polyethylene Glycol 6000 and Cocoa butter: Polyethylene Glycol 9000) were prepared in the ratio of 1:9 to 9:1.Cocoa butter was taken alone and used as standard. These base combinations were evaluated for optimization of base using parameters like melting point and liquefaction time. The optimized base (Cocoa butter: Polyethylene Glycol 6000 with ratio of1:9 and Cocoa butter: Polyethylene Glycol 9000 with ratio of1:9) was then formulated into Colon Targeted Suppository of Mesalazine. Polyethylene glycol 400 was added in combination of bases which was used as plasticizer to increase its flexibility which was added in the concentration of 15, 30 and 45%. Displacement value was then calculated to formulate suppository. These formulated colon targeted Mesalazine suppository were evaluated with parameters such as weight variation, hardness, melting point, liquefaction time, content uniformity, and dissolution test. The F3 batch was selected as optimized formulation and was found superior. The F3 formulation shows high drug release of 94.31% and less dissolution time of 30 minutes from six formulation batches; Hence showing better results than other formulations. When F3 formulation was compared with marketed formulation, it gives highest percent drug release than marketed formulation. The results of stability studies showed that F3 has no significant change in drug content, melting point, hardness, liquefaction time and dissolution profile of suppositories after storing them for 90 days at refrigeration temperature.

KEYWORDS: *Mesalazine, Ulcerative Colitis, Colon Targeted Drug Delivery System, Suppository.*

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INTRODUCTION

Targeted drug administration into the lower channel, specifically the large intestine, is understood as colon transport (i.e. Colon).Targeted drug transport implies selective and effective localization of drug into the goal at healing concentrations with constrained get admission to non-target sites. A focused drug transport gadget is desired in pills having instability, low solubility and brief half-life. Targeted transport of medication to the colon is often to reap one or greater of 4 objectives-To lessen dosing frequency, to postpone transport to the colon to reap excessive nearby concentrations within side the remedy of illnesses of the distal gut, to postpone transport to a time suitable to cope with acute stages of disease (Chronotherapy), to supply to an area this can be much less antagonistic metabolically eg. to facilitate absorption of acid and enzymatically labile materials, particularly peptides. The colon makes up the longest a component of the massive gut. It starts from the caecum on the valve and ends within side the rectum.

The colon is prepared 1.five meters lengthy and frames the convolute of the tiny gut within side the belly cavity. However it should be shortened and lie pretty flexibly just in case of an incomplete rotation of the umbilical loop for the duration of embryogenesis. The colon is subdivided into four parts: ascending, transverse, descending and colon. The colon lays secondary retro peritoneal at the correct facet of the belly cavity and movements within the direction of the correct colic flexure at the bottom facet of the liver. From there the colon runs intra peritoneal within the direction of the spleen forming the left colic flexure. This component is attached to the posterior belly wall via way of means of the mesocolon and is consequently very flexible. Beginning on the left colic flexure the colon proceeds downwards secondary retroperitoneal on the left belly wall and adjustments over to the S shaped colon within side the left iliac fossa. Because the colon lays intra peritoneal it's a mesocolon further. This final an element of the colon ends within side the rectum at the height of S2-S3.Inflammatory bowel disorder (IBD) is an idiopathic disease resulting from immune response to host intestinal micro flora. The fundamental quantity IBD is often accustomed 2 bows disorder having many similarities however the situations commonly have unique morphological appearance. These two situations are inflammatory bowel disease and Crohn's disorder. Crohn's disorder may additionally contain any a part of the digestive tube however have an impact on most typically 15-25 cm of the terminal ileum which may also additionally amplify into the caecum and sometimes into the colon. Both inflammatory bowel disease and Crohn's disorder commonly contain severe diarrhoea, belly pain, and fatigue and weight loss. Colitis is an inflammatory bowel disorder (IBD) that reasons infection and ulcers (sores) to your alimentary canal. Inflammatory bowel disease impacts the innermost lining of your big intestine (colon) and rectum. Symptoms commonly increase over time, alternatively than suddenly. It develops from variety from moderate to severe. Having inflammatory bowel disease places a patient at extended threat of growing carcinoma. A drug could also be dropped at the colon thru the oral, or the rectal route. Drug while administered orally undergoes first by skip metabolism which does now not attain web website online of motion i.e. colon. So to stay removed from first by skip metabolism, drug is run rectally that's formulated in suppository. Suppositories are strong dosage bureaucracy meant for insertion in to border cavities or orifices (Rectum, Vagina & Urethra) wherein they soften or dissolved & exert localized or systemic effect. Drugs will be administered in suppository shape for both nearby or systemic effects. Such motion relies upon on the character of the drug, its concentration, and also the charge of absorption. Emollients, astringents, antibacterial dealers, steroids, and nearby an aesthetics are disbursed in suppository for treating nearby situations Analgesics, antispasmodics, sedatives, tranquilizers, and antibacterial dealers are disbursed in suppository for systemic motion.

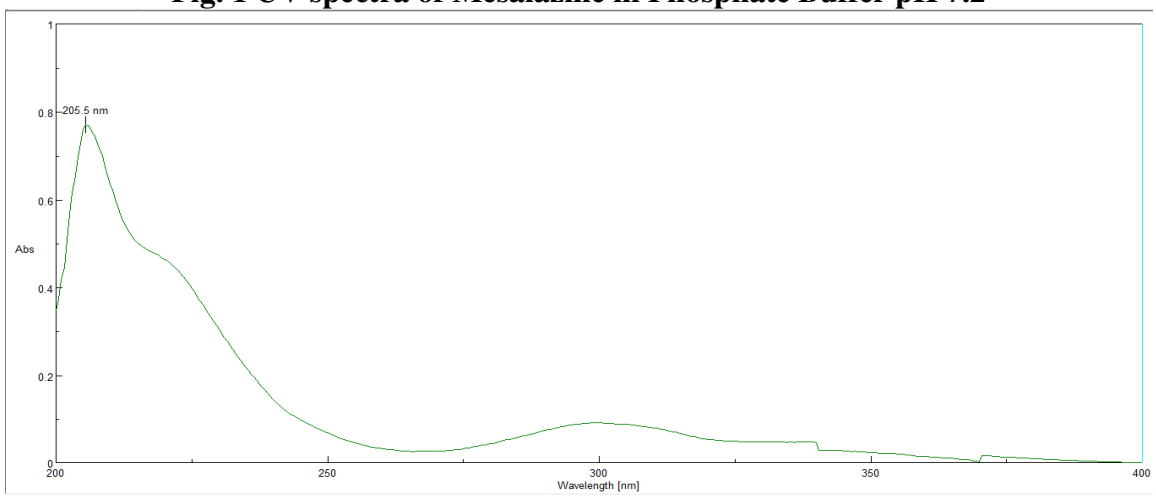
MATERIALS AND METHODS:

Mesalazine was obtained from Yarrow Chem Products, Mumbai. Cocoa butter, Polyethylene Glycol 400, Polyethylene Glycol 6000, Polyethylene Glycol 9000 was obtained from Research Lab Fine Chem. Industry, Mumbai. Other excipients such a Tween 80 and Methyl Paraben was also obtained from Research Lab Fine Chem. Industry, Mumbai.

Calibration of Mold and Displacement Value

Calibration is performed for each suppository form with the usual criteria for making medicines. The right amount of suppository was first manufactured of molded suppositories from the base material only. After removing from the mold, weigh the suppository and add it to the total weight. The average weight of each suppository is recorded. The molds that are calibrated of 1.01gms to 1.32gms.

Fig. 1 UV spectra of Mesalazine in Phosphate Buffer pH 7.2



Pre formulation Studies of Base

Base optimization was done to select best combinations of bases by applying evaluation parameters like melting point and liquefaction time to prepare colon targeted suppository of Mesalazine. The various combinations of Cocoa Butter, Polyethylene Glycol 6000 and Polyethylene Glycol 9000 were taken in the ratio of 9:1 to 1:9 respectively. These combinations of bases were evaluated and best combinations of bases was selected to manufacture colon targeted suppository of Mesalazine.

Table 1: Base Optimization of Suppository Base

Bases	Ratio	Melting point(°C)	Liquefaction time(mins)
Cocoa Butter	-	31	3
Cocoa Butter: **Polyethylene Glycol 6000**	9:1	32	3
	8:2	35	4
	7:3	36	8
	6:4	44	9
	5:5	49	14
	4:6	51	21
	3:7	55	37
	2:8	56	48
	1:9	59	51
Cocoa Butter: **Polyethylene Glycol 9000**	9:1	35	4
	8:2	38	15
	7:3	41	19
	6:4	44	37
	5:5	49	51
	4:6	52	59
	3:7	57	67
	2:8	61	77
	1:9	63	84

Preparation of Suppository

During base optimization from combinations of different bases prepared by fusion method, the best batch was selected by evaluating base combinations using parameters like melting point and liquefaction time. The best batch of Cocoa butter and Polyethylene glycol 6000 and Cocoa butter and Polyethylene glycol 9000 of ratio 9:1 was selected. Total six batches for Colon Targeted Suppository of Mesalazine was prepared by first melting the bases separately, later adding Mesalazine to the melted bases which were thoroughly mixed to form a homogenized mixture. Lastly various excipients like Polyethylene Glycol 400, Tween 80, Methyl Paraben were added and poured in the lubricated mould to form suppository.

Table 2: Formulation of Colon Targeted Suppository of Mesalazine

Formulations	F1	F2	F3	F4	F5	F6
Ingredients	*Unit formula (mg per suppository)*					
Mesalazine	400	400	400	400	400	400
Cocoa butter	521.1	507.6	494.1	521.1	507.6	494.1
Polyethylene glycol 6000	57.9	56.4	54.9	-	-	-
Polyethylene glycol 9000	-	-	-	57.9	56.4	54.9
Polyethylene Glycol 400	15	30	45	15	30	45
Tween 80	5	5	5	5	5	5
Methyl paraben	1	1	1	1	1	1
Total	1000	1000	1000	1000	1000	1000

EVALUATION OF COLON TARGETED SUPPOSITORY OF MESALAZINE

Table 3: Evaluation of Colon Targeted Suppository of Mesalazine

Sr.no	Parameter studied	Formulation					
		F1	*F2*	*F3*	*F4*	*F5*	*F6*
1	Hardness test(g/cm^2)	3.8±0.16	3.7±0.13	3.5±0.09	4.0±0.06	3.8±0.09	3.7±0.08
2	Melting point(^{o}C)	39.5±1.02	38.5±1.03	37±1.16	41±1.05	40±1.12	39.5±1.09
3	Liquefaction time(mins)	9±0.05	7±0.04	6±0.10	11±0.07	9±0.02	8±0.09
4	Weight variation(g)	1.4±0.06	1.3±0.02	1.5±0.04	1.7±0.08	1.4±0.09	1.6±0.05
5	Drug content (%)	96.19±0.15	95.32±1.93	95.87±1.78	96.62±0.19	95.65±1.56	96.48±0.85

General appearance

Suppositories were taken randomly from batches for visual evaluation which include parameter like colour, odour, surface characteristics.

Hardness test

Monsanto hardness tester was used to evaluate the hardness of suppository.

Melting point determination

Determination of melting point was done by selecting three suppositories from each batches which was then placed in the water bath containing phosphate buffer pH7.2 with 37^o C. The temperature was noted when the whole suppository is melted.

Liquefaction time

This test was performed in burette having broad opening one end and a narrow on the other. Burette was filled with 5 ml phosphate buffer (pH 7.2) which is placed in a water bath having 37°C.A suppository was placed inside the burette from the broad end which was then pushed to the narrow end. A thin glass rod was placed on the top of suppository. The time for glass rod to penetrate the suppository was noted.

Weight variation

Suppositories were weighed individually and its mean was calculated. Weight variation limit of suppositories should no more than two suppositories should deviate by more than 5% of the average weight but should not deviate more than 7.5%

Drug content percentage

Assay was done by placing a suppository in 700 ml of phosphate buffer (pH 7.2) that was maintained at 37°C till it melted. 1 ml of sample was withdrawn and then diluted into 50 ml with phosphate buffer which was then determined by UV visible spectrophotometer by measuring its absorbance at 205nm.

In-vitro release profile

The in-vitro releases of various formulation of colon targeted suppository of Mesalazine were studied with apparatus known as dissolution test apparatus type I basket (LABINDIA, Martix Techno Chem, India).A suppository from each batch was placed in 900 ml phosphate buffer (pH 7.2, temperature 37°C) at a 50 rpm. Aliquots of 10 ml was taken at various time intervals which was then filtered with Whatman No. 1 filter paper that is used for quantitative analysis of Mesalazine by UV visible spectrophotometer at 205.5 nm. Each sample was replaced with 10 ml fresh buffer. The cumulative percentage of drug release was calculated and plotted versus time.

Stability study

The prepared colon targeted suppository of Mesalazine were placed and stored at ambient conditions, 4^{o}C for a period of 90 days. Each suppository was weighed and wrapped in a aluminium foil and put at above specified conditions in a refrigerator for three months. After each month, suppository sample was analysed for hardness, melting point, liquefaction time, dissolution and drug content

Table 4: Stability Studies of Formulation F3

Storage period	Stored at 4^{0}C with no control of RH *Formulation F3*				
	Hardness (Kg/cm^2)	*Melting point(^{o}C)*	*Liquefaction time(min)*	*Drug content%*	*Drug release%*
Initial	3.5±0.02	37±1.23	6±0.01	95.87±1.45	94.31±0.05
After 2 month	3.4±0.01	36±1.25	5±0.03	94.11±1.23	93.45±0.12
After 3 month	3.4±0.06	35±10.34	5±0.02	93.54±1.32	93.12±0.10

RESULTS AND DISCUSSION:

The drug sample of Mesalazine was evaluated for its organoleptic properties and it was found that the drug sample of Mesalazine complies with standard of IP. The Melting point of received drug sample of Mesalazine was determined and it was found in the range of 283-285^{o}C which complies with the standard of IP indicating purity of the Mesalazine. The standard solution of Mesalazine was scanned in the range of 200-400nm and absorbance was found to be 205.5 nm. The calibration curve's linear regression equation and correlation coefficient was found to be y = 0.097x + 0.0186 and R^2 = 0.995

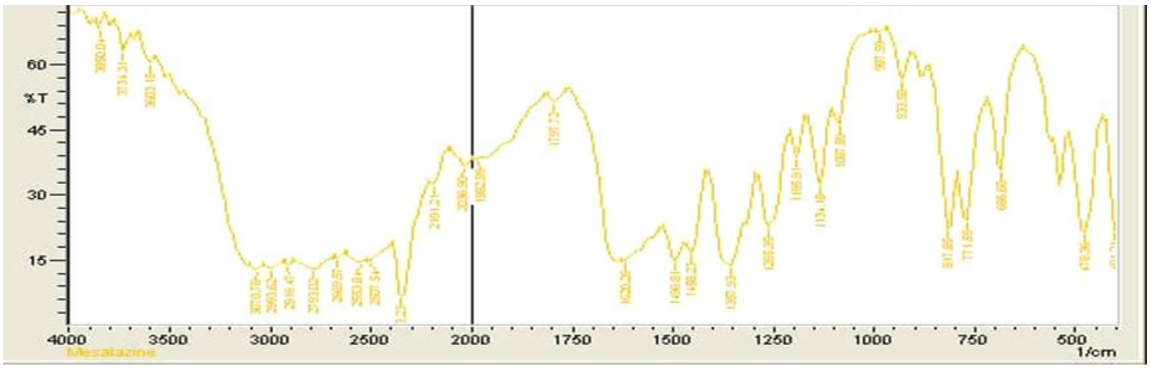


Fig. 2 FTIR Studies of Mesalazine

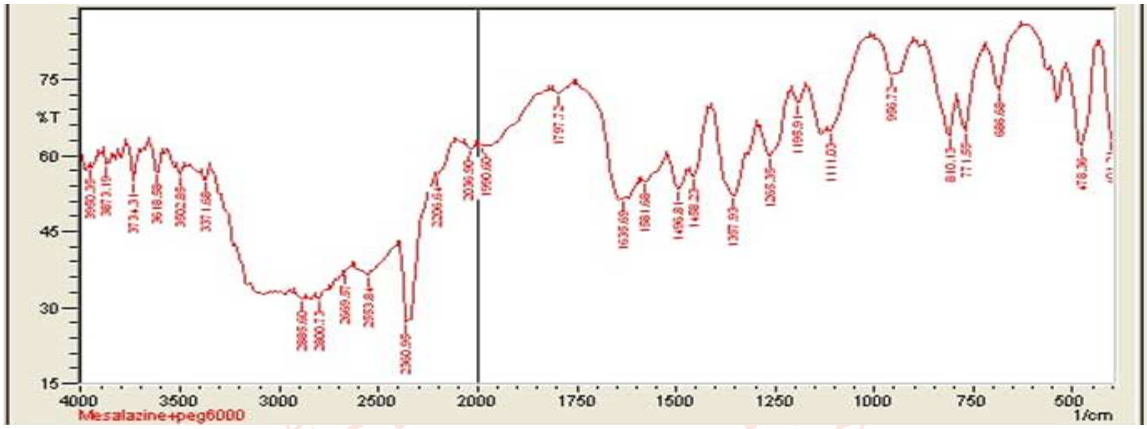


Fig. 3 FTIR Studies of Mesalazine+ Polyethylene Glycol 6000

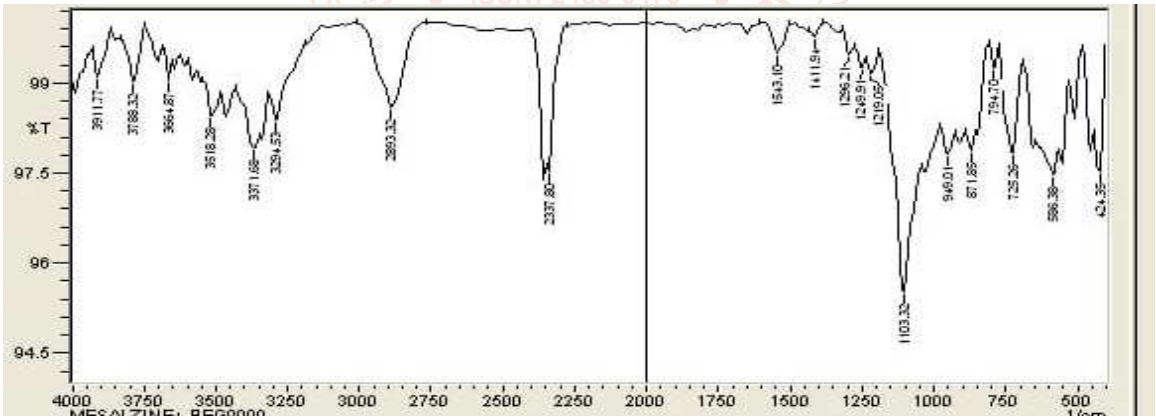


Fig. 4 FTIR Studies of Mesalazine+ Polyethylene Glycol 9000

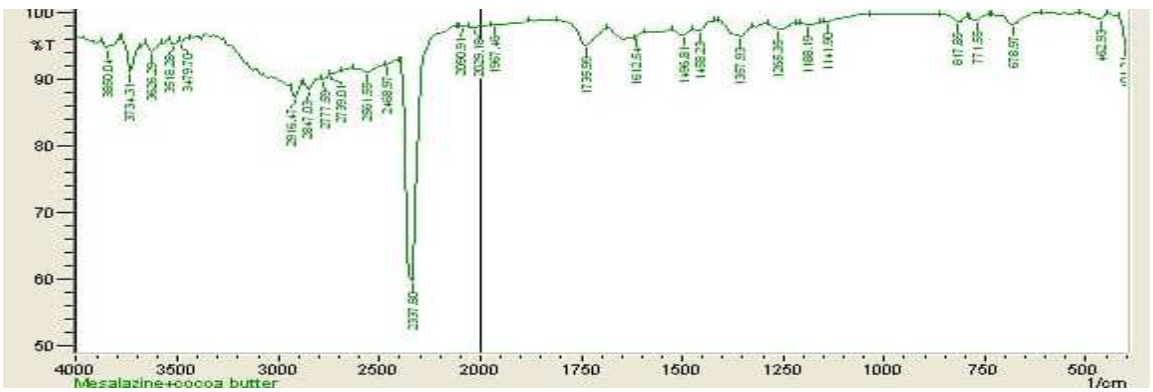


Fig. 5 FTIR Studies of Mesalazine+Cocoa butter

The combination of bases were evaluated and bases combination 9:1 i.e. Cocoa Butter: Polyethylene glycol 6000 and 9:1 i.e. Cocoa Butter: Polyethylene glycol 9000 was found best and it was selected for formulation of the colon targeted suppository of Mesalazine. The suppositories are evaluated by using Monsanto Hardness. Tester Hardness of formulated colon targeted suppository of Mesalazine was in the range of 3.5±0.13- 4.0±0.06 g/ cm^2. The obtained hardness range showed good mechanical strength with an ability to withstand physical and mechanical stress conditions. The melting point of formulated colon targeted suppository of Mesalazine was carried out and its melting point was found in the range of 37±1.16 - 41±1.05^o C. The liquefaction time of formulated colon targeted suppository of Mesalazine was carried out and its liquefaction time was found in the range of 6±0.10- 11±0.07min. This states that the time required for suppositories to liquefy. The weight variation of formulated colon targeted suppository of Mesalazine was carried out and its weight variation was found in the range of 1.3±0.02 - 1.7±0.08 mg. Suppository were obtained in the range with acceptable weight variations as per Pharmacopoeia specifications, limit of ±5%. The suppositories were evaluated by using assay method. The drug content was obtained in the acceptable limit. The drug content was found in the range of 95.32±1.93-96.62±0.19 %w/w. The found range was within the specified limit as per Pharmacopoeia.

Table 5: *In vitro* Cumulative % Drug Release from Suppository

Time (min)	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	17.29	26.12	40.93	19.06	25.13	15.45
20	35.37	40.86	68.25	37.21	59.25	49.36
30	60.12	70.28	94.31	67.29	76.13	66.28
45	71.37	83.41	-	81.28	89.23	91.69
60	90.69	-	-	-	-	-

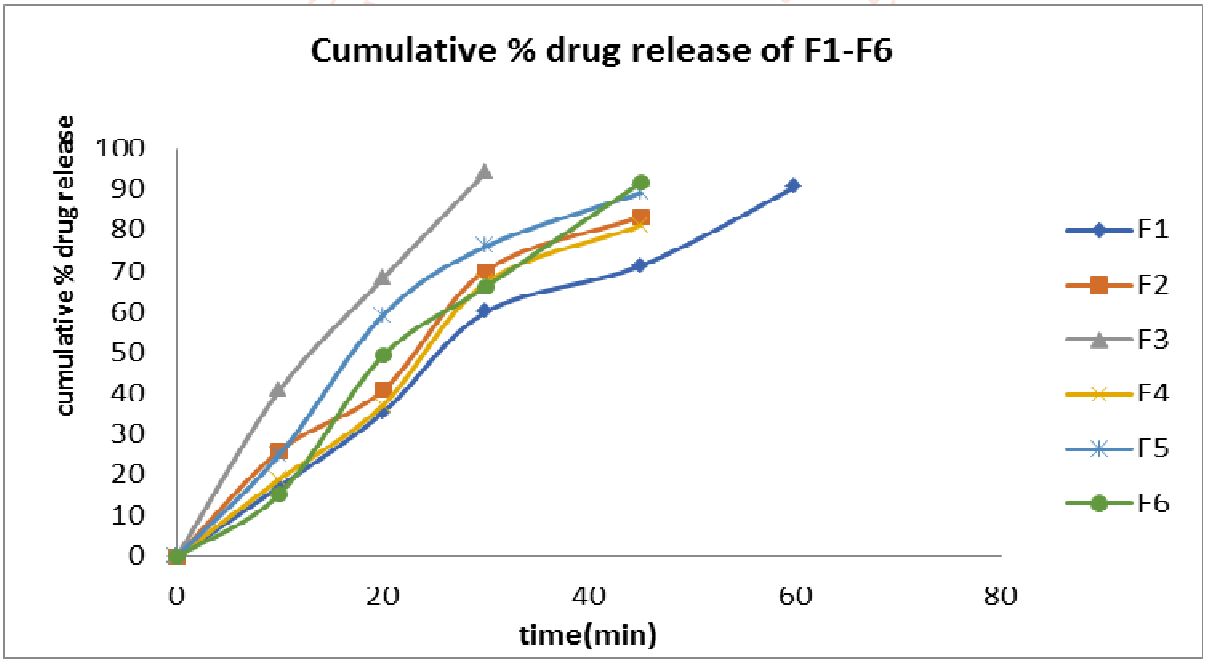


Fig. 6 Cumulative % Drug Release of F1-F6 Formulations

The rapid dissolution was observed in formulation F3 releases 94.31% at the end of 30 minutes. Rapid dissolution might be due to high concentration of plasticizer. The drug release was completely achieved in shorter duration of time. In cumulative percent drug release study, F3 batch showed higher percent of drug release compared to other formulations at the end of 30 minutes. Therefore it was concluded that the F3 is best batch as because of lesser disintegration time and highest percentage of drug release at the end of 30 min among all the formulations. The results of stability testing are shown using parameters like melting point, hardness, liquefaction time, drug content and dissolution profile of colon targeted suppository of Mesalazine after storing them for 90 days at refrigeration temperature.

CONCLUSION:

Overall, the results concluded that suitable optimized formulation of F3 of Mesalazine with Cocoa Butter: Polyethylene Glycol 6000 prepared by fusion method improved its solubility and dissolution rate. It was decided to prepare colon targeted suppository of Mesalazine by fusion method. In the formulation of colon targeted suppository of Mesalazine, Cocoa butter, Polyethylene Glycol 6000, Polyethylene Glycol 9000 as base. Tween 80, Polyethylene Glycol 400 and Methyl Paraben are used as additives.Prior to formulation of colon targeted Mesalazine suppository, the bases were evaluated for melting point, liquefaction time. Polyethylene glycol 400 was used as plasticizer to increase its flexibility which was taken in the concentration of 15, 30 and 45%. Polyethylene glycol 400 with the concentration of 45% was found to increase its flexibility than other concentrations when used in combination of bases of Cocoa butter: Polyethylene glycol 6000.The optimized formulation of colon targeted suppository of Mesalazine were evaluated for weight variation, hardness, melting point, liquefaction time, content uniformity and in vitro drug release. From above results it can be concluded that the fusion method can be used to enhance the solubility, dissolution rate and rectal bioavailability of water insoluble drugs. The optimized suppository formulation was compared with conventional marketed suppository for drug release profiles. This formulation shows high drug release and less dissolution time when compared to the conventional commercial suppository formulation. The results of stability studies showed that F3 has no significant change in drug content, melting point, hardness, liquefaction time and dissolution profile of suppository after storing them for 90 days at refrigeration temperature.

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References

[1] Haidy abass, rabab kamel, ahmed abdelbary, metronidazole bioadhesive vaginal suppositories: formulation, in vitro and in vivo evaluation, International Journal of Pharmacy and Pharmaceutical Sciences Vol 4, Issue 1, 2012.

[2] M. Gautam, D. Santhiya, In-situ mineralization of calcium carbonate in pectin based edible hydrogel for the delivery of protein at colon, J. Drug Deliv. Sci. Technol. 53 (2019) 101137.

[3] P. V. Turner, The role of the gut microbiota on animal model reproducibility, Anim. Model. Exp. Med. 1 (2018) 109–115.

[4] A. S. Aguirre, D. Teijeiro-Osorio, M. Rosa, I. S. Coulter, M. J. Alonso, D. J. Brayden, Current status of selected oral peptide technologies in advanced preclinical development and in clinical trials, Adv. Drug Deliv. Rev. 106 (2016) 223–241.

[5] P. Chaubey, M. Momin, S. Sawarkar, Significance of ligand-anchored polymers for drug targeting in the treatment of colonic disorders, Front. Pharmacol. 10 (2020) 1–14.

[6] B. Sarmento, J. Das Neves, Chitosan-Based Systems for Biopharmaceuticals: Delivery, Targeting and Polymer Therapeutics (2012)

[7] G. Kaur, V. Rana, S. Jain, A. K. Tiwary, Colon delivery of budesonide: evaluation of chitosan–chondroitin Sulfate Interpolymer complex, AAPS PharmSciTech 11 (2010) 36–45.

[8] S. Das, A. Chaudhury, K. Y. Ng, Preparation and evaluation of zinc-pectin-chitosan composite particles for drug delivery to the colon: role of chitosan in modifying in vitro and in vivo drug release, Int. J. Pharm. 406 (2011) 11–20.

[9] Sanguineti G, Franzone P, Marcenaro M, Foppiano F and Vitale V: Sucralfate versus mesalazine versus hydrocortisone in the prevention of acute radiation proctitis during conformal radiotherapy for prostate carcinoma. A randomized study. Strahlenther Onkol 179: 464‑470, 2003.

[10] Mendenhall WM, McKibben BT, Hoppe BS, Nichols RC, The prevalence of chronic radiation enteritis following radiotherapy for cervical or endome Henderson RH and Mendenhall NP: Management of radiation proctitis. Am J Clin Oncol 37: 517‑523, 2014.

[11] Ruiz‑Tovar J, Morales V, Hervás A, Sanjuanbenito A, Lobo E and Martínez‑Molina E: Late gastrointestinal complications after pelvic radiotherapy: Radiation enteritis. Clin Transl Oncol 11: 539‑543, 2009

[12] Dziki Ł, Kujawski R, Mik M, Berut M, Dziki A and Trzciński R: Formalin therapy for hemorrhagic radiation proctitis. Pharmacol Rep 67: 896‐900, 2015.

[13] McElvanna K, Wilson A and Irwin T: Sucralfate paste enema: A new method of topical treatment for haemorrhagic radiation proctitis. Colorectal Dis 16: 281‐284, 2 014

[14] Hille A, Schmidberger H, Hermann RM, Christiansen H, Saile B, Pradier O and Hess CF: A phase III randomized, placebo‐controlled, double‐blind study of misoprostol rectal suppositories to prevent acute radiation proctitis in patients with prostate cancer. Int J Radiat Oncol Biol Phys 63: 1488‐1493, 2005.

[15] Canard JM, Védrenne B, Bors G, Claude P, Bader R and Sondag D: Long term results of treatment of hemorrhagic radia‐tion proctitis by argon plasma coagulation. Gastroenterol Clin Biol 27: 455‐459, 2003 (In French).

[16] Pinto A, Fidalgo P, Cravo M, Midões J, Chaves P, Rosa J, dos Anjos Brito M and Leitão CN: Short chain fatty acids are effective in short‐term treatment of chronic radiation proctitis: Randomized, double‐blind, controlled trial. Dis Colon Rectum 42: 788‐796, 1999.

[17] Talley NA, Chen F, King D, Jones M and Talley NJ: Short‐chain fatty acids in the treatment of radiation proctitis: A randomized, double‐blind, placebo‐controlled, cross‐over pilot trial. Dis Colon Rectum 40: 1046‐1050, 1997.

[18] Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S and Keshavarzian A: Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. Am J Gastroenterol 96: 1080‐1084, 2001.

[19] Sahakitrungruang C, Thum‐Umnuaysuk S, Patiwongpaisarn A, Atitthar nsakul P and Rojanasaku l A: A novel treat ment for haemor‐rhagic radiation proctitis using colonic irrigation and oral antibiotic administration. Colorectal Dis 13: e79‐e82, 2011.

[20] Hille A, Christiansen H, Pradier O, Hermann RM, Siekmeyer B, Weiss E, Hilgers R, Hess CF and Schmidberger H: Effect of pentoxifylline and tocopherol on radiation proctitis/enteritis. Strahlenther Onkol 181: 60 6 ‐614, 2005.

[21] Wang L, Zhang ZZ, Tu XH, Zou ZD, Liu JH and Wang Y: Safety and efficacy of Qingre Buyi Decoction in the treatment of acute radiation proctitis: A prospective, randomized and controlled trial. Chin J Integr Med 15: 272‐278, 2009.

[22] Pigò F, Bertani H, Manno M, Mirante VG, Caruso A and Conigliaro RL: Radiofrequency ablation for chronic radia‐tion proctitis: Our initial experience with four cases. Tech Coloproctol 18: 1089‐1092, 2014.

[23] Dray X, Battaglia G, Wengrower D, Gonzalez P, Carlino A, Camus M, Adar T, Pérez‐Roldán F, Marteau P and Repici A: Radiofrequency ablation for the treatment of radiation proctitis. Endoscopy 46: 970‐976, 2014.

[24] Hortelano E, Gómez‐Iturriaga A, Ortiz‐de‐Zárate R, Zaballa M, Barturen Á, Casquero F, San‐Miguel Í, Carvajal C, Cacicedo J, Del‐Hoyo O, et al: Is argon plasma coagulation an effective and safe treatment option for patients with chronic radiation proctitis after high doses of radiotherapy? Rev Esp Enferm Dig 106: 165 ‐170, 2014.

[25] Canard JM, Védrenne B, Bors G, Claude P, Bader R and Sondag D: Long term results of treatment of hemorrhagic radia‐tion proctitis by argon plasma coagulation. Gastroenterol Clin Biol 27: 455‐459, 2003 (In French).

[26] Karamanolis G, Triantafyllou K, Tsiamoulos Z, Polymeros D, Kalli T, Misailidis N and Ladas SD: Argon plasma coagulation has a long‐lasting therapeutic effect in patients with chronic radiation proctitis. Endoscopy 41: 529‐531, 2009.

[27] Koessler T, Servois V, Mariani P, Aubert E and Cacheux W: Rectal ulcer: Due to ketoprofen, argon plasma coagulation and prostatic brachytherapy. World J Gastroenterol 20: 17244‐17246, 2014. 31. Ravizza D, Fiori G, Trovato C and Crosta C: Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radiation‐induced proctopathy. Gastrointest Endosc 57: 519‐525, 2003.

[28] De Parades V, Etienney I, Bauer P, Bourguignon J, Meary N, Mory B, Sultan S, Taouk M, Thomas C and Atienza P: Formalin application in the treatment of chronic radiation‐induced hemorrhagic proctitis‐an

effective but not risk‐free procedure: A prospective study of 33 patients. Dis Colon Rectum 48: 1535‐1541, 2005.

[29] Tsujinaka S, Baig MK, Gornev R, de la Garza C, Hwang JK, Sands D, Weiss EG, Nogueras JJ, Efron J, Vernava AM III and Wexner SD: Formalin instillation for hemorrhagic radiation proctitis. Surg Innov 12: 123‐128, 2005.

[30] Allen S, Kilian C, Phelps J and Whelan HT: The use of hyperbaric oxygen for treating delayed radiation injuries in gynecologic malignancies: A review of literature and report of radiation injury incidence. Support Care Cancer 10: 2467‐2472, 2012.

[31] Oscarsson N, Arnell P, Lodding P, Ricksten SE and Seeman‐Lodding H: Hyperbaric oxygen treatment in radiation‐induced cystitis and proctitis: A prospective cohort study on patient‐perceived quality of recovery. Int J Radiat Oncol Biol Phys 87: 670‐675, 2013.