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FORMULATION AND EVALUATION OF A pH DEPENDENT MULTI-PARTICULATE COLON TARGETED DRUG DELIVERY SYSTEM USING POWDER LAYERING TECHNOLOGY OF KETOPROFEN

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Keywords:

Ketoprofen, Powder layering technology, Eudragit S100, Eudragit L100

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ABSTRACT: Multiparticulates consist of discrete, small, multiple unit systems of active pharmaceutical ingredients exhibiting the desired drug release pattern. The present work is concerned with the formulation and evaluation of a pH-dependent multiparticulate colon targeted drug delivery system of ketoprofen, a well established anti-inflammatory drug used in the management of inflammatory bowel disease. The reason for carrying out this study was to release the drug at a targeted site of the large intestinal region of the gastrointestinal tract on the basis of pH variability and to improve patient compliance. The drug-loaded pellets were fabricated using powder layering technology and thereafter pH-dependent multiparticulates were prepared by employing a mix polymeric coating of pH-dependent Eudragit S100 and Eudragit L100 polymers over the drug-loaded pellets. Different ratios of these pH-dependent polymers were used in the formulations of the coated drug-loaded pellets. The developed pellets were assessed for technical parameters such as drug entrapment efficiency, *in-vitro* dissolution study, scanning electron microscopy, FTIR, and DSC study. The *in-vitro* release kinetics reveals that the optimum formulation batch follows anomalous transport towards zero-order kinetics, which is further confirmed by the Korsmeyer-Peppas model.

INTRODUCTION: Oral administration of drugs still remains a widely accepted and convenient route for the delivery of various drugs. Continuous developments in polymer technology have enabled formulation technologists to develop pH-dependent multiparticulate drug delivery systems with improved gastric irritation and patient compliance as many of the patients faces the problem of acidity. To overcome this problem, these coated pellets have been prepared to release the drug at a desirable site of the colon [1].

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A targeted drug administration into the large intestine is most desirable for the local management and treatment of a wide spectrum of large bowel diseases such as colitis ulcerosa, abdominal pain, inflammatory granulomatous bowel symptoms, colonic infection, colonic cancer, management of colonic pathologies, and systemic targeting of protein and peptide therapeutics [2].

The colon therapeutic system (CTS) should be capable of preserving the drug during its transportation to the large intestine area, drug release and absorption should not occur in the stomach as well as in the small intestine i.e. not only the drug should not break down in either of these two early gastrointestinal sites but, it should also permit the bioactive agent to get released and absorbed once CTS reaches the colon [3].

Multiparticulate subunits are delivered by filling them inside a capsule or sachet. A multiparticulate system consists of a multiplicity of the plurality of a number of small independent spherical particles with a diameter of 0.05-2.00 mm. As multi-particulates comprises of individual active subunits, so they are called multiple unit system [4].

In the powder layering technique, the dry powdered drug is used for layering. This process is usually carried out in a conventional tablet coating pan. Initially, the nonpareil seeds are charged into a rotating pan and these are then wetted by spraying an adhesive binder solution. As the wet seeds reach the front end of the pan, the powdered drug is added in the swirl, which then adheres to the wetted nonpareil seeds [5].

The inflammatory bowel syndrome (IBS) primarily includes Crohn's disease and colitis gravis. Crohn's disease is an inflammatory bowel disease that causes inflammation anywhere along the lining of the gastrointestinal path, while colitis gravis causes long-lasting inflammation in the gastrointestinal tract mainly large intestine [6]. IBS has an effect on about 11% of the population throughout the world. These people have greater levels of worry and poor quality of life. The prevalence of IBS is predominantly seen in the female population. People suffering from inflammatory bowel disease are highly subjected to have other functional disorders and undergo surgical procedures more than the general population [7].

Ketoprofen is a non-steroidal, anti-inflammatory drug with the analgesic property. Ketoprofen has an oral bioavailability of 90%, a short biological half-life (2-4 h) and gets rapidly absorbed following oral administration. The chemical name of ketoprofen is 2-(3-benzoylphenyl)-propionic acid. The structural formula of ketoprofen is $C_{16}H_{14}O_3$. It is metabolized by glucuronidation of the Carboxylic acid. The anti-inflammatory action of ketoprofen is because of inhibition of leukocyte migration and inactivation of cyclooxygenase, leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of prostaglandin precursors is responsible for the analgesic effect of Ketoprofen [8]. It is clinically used to treat chronic inflammatory disorders such as inflammatory bowel syndrome [9].

MATERIALS AND METHODS:

Materials: Ketoprofen was obtained as a gift sample from BEC Chemicals, Mumbai. Eudragit S100 and Eudragit L100 were gifted by Evonik Private Ltd, Mumbai. Dibutyl phthalate was obtained from HiMedia Laboratories Private Ltd. Mumbai. Nonpareil sugar seeds (30#) were gifted by Signet Chemical Corporation Private Ltd. Ethanol and Acetone were purchased from Changshu Hong sheng Fine Chemicals Co. Ltd. All the other chemicals used were of analytical grade.

Methods:

Drug-Polymer Physical Compatibility Studies:

FTIR: The FTIR study of the samples *i.e.* the pure drug, polymer physical mixture (1:1) and optimized formulation batches were assessed by using a Fourier-transform-infrared spectrophotometer using KBr disc method (Model Shimadzu IR Affinity-1).Samples were analyzed in the scanning range of 4000-400 cm^{-1} to obtain the FTIR Spectra [10].

Differential Scanning Calorimetry (DSC) Study: DSC has been used for thermal analysis of drug, individual polymers, drug-polymer physical mixture, and optimized formulation batches. It is carried out by using Differential Scanning Calorimeter (Perkin Elmer) to evaluate drug-polymerr interaction. Bioactive agent, polymers, active agent polymer physical mixture (1:1) as well as drug loaded pellets was triturated individually to obtain finely divided powder and the powder was finally passed through a sieve no. 120. Accurately weighed amount of sample (5- 10 gm) were taken by using a single pan electronic micro balance and heated in a sealed aluminum pan at a specified rate and the temperature range was from 25-500 °C under a nitrogen flow of 20ml/ min [11].

Preparation of Multiparticulate System:

Preparation of Standard Stock Solution: 10 mg of ketoprofen pure drug was dissolved in 10 ml of pH 1.2 or 0.1 N HCl (SGF), pH 6.8 phosphate buffer (SIF) and pH 7.4 phosphate buffer (SCF), from this 10 ml of solution was taken, and the volume was adjusted to 10 ml with respective phosphate buffer and suitable dilutions were made to get the concentrations in the range of 0.5 to 15 µg/ml. The absorbance of the above dilutions was measured at 260 nm by using UV- spectro-photometer [12].

Preparation of Ketoprofen loaded Pellets by Powder Layering Technique: 100 mg drug was weighed as per the recommended dosage of ketoprofen. Precisely weigh the amount of nonpareil seeds needed. The nonpareil seeds were dried at 35 °C to eliminate moisture. These nonpareil seeds were then transferred to a tablet-coating pan, having a bed temperature of 35 °C. A 5% PVP K-30 solution in water: isopropyl alcohol (30:70) was used as a binder solution. The binder solution was sprayed with the help of a spray gun till the bed became wet and then after immediate talc and then the powdered drug was added over the wet bed of the pellets. Mixing was done with great care to get the optimum loading of the drug. After the preparation of drug-loaded pellets, each batch of the loaded pellets was dried inside a hot air oven at 45 °C for 30 min [13].

TABLE 1: COMPOSITION OF KETOPROFEN DRUG LOADED PELLETS

Formulation	Non par-il (mg)	Ketoprofen (mg)	Eudragit S100: Eudragit L100 (Ratio)	Level of coating (%)	Talc (%w/w)	DBP (% w/w)
F1	400mg	100mg	1:1	10%	5% w/w	2% w/w
F2	400mg	100mg	1:1	15%	5% w/w	2% w/w
F3	400mg	100mg	1:1	20%	5% w/w	2% w/w
F4	400mg	100mg	1:4	10%	5% w/w	2% w/w
F5	400mg	100mg	1:4	15%	5% w/w	2% w/w
F6	400mg	100mg	1:4	20%	5% w/w	2% w/w
F7	400mg	100mg	1:3	10%	5% w/w	2% w/w
F8	400mg	100mg	1:3	15%	5% w/w	2% w/w
F9	400mg	100mg	1:3	20%	5% w/w	2% w/w
F10	400mg	100mg	2:3	10%	5% w/w	2% w/w
F11	400mg	100mg	2:3	15%	5% w/w	2% w/w
F12	400mg	100mg	2:3	20%	5% w/w	2% w/w
F13	400mg	100mg	3:2	10%	5% w/w	2% w/w
F14	400mg	100mg	3:2	15%	5% w/w	2% w/w
F15	400mg	100mg	3:2	20%	5% w/w	2% w/w
F16	400mg	100mg	3:1	10%	5% w/w	2% w/w
F17	400mg	100mg	3:1	15%	5% w/w	2% w/w
F18	400mg	100mg	3:1	20%	5% w/w	2% w/w
F19	400mg	100mg	4:1	10%	5% w/w	2% w/w
F20	400mg	100mg	4:1	15%	5% w/w	2% w/w
F21	400mg	100mg	4:1	20%	5% w/w	2% w/w

TABLE 2: INGREDIENTS OF COATING SOLUTION

Eudragit S100 and Eudragit L100 ratio	Eudragit S 100 (gm)	Eudragit L 100 (gm)
1:1	5	5
1:4	2	8
1:3	2.5	7.5
2:3	4	6
3:2	6	4
3:1	7.5	2.5
4:1	8	2

Preparation of Coating Solution: The required quantity of Eudragit L100 and Eudragit S100 were dissolved in a previously plasticized mix solvent of acetone and isopropyl alcohol and stirred with a magnetic stirrer to make the coating solution homogeneous. Dibutyl phthalate was used in the above coating solution as a plasticizer (2% w/w of the dry weight of the polymer). After obtaining a homogeneous coating solution, the coating of the uncoated drug-loaded pellets was performed with utmost care. The theoretical percentage of weight gain (TWG) while applying the mix polymeric coating over the drug-loaded pellets was kept constant at three levels *i.e.* 20, 15, and 10% w/v. The ratio of two methacrylic acid and methyl methacrylate copolymer mixtures in the different batches of the coating solutions were 1:1, 1:4, 1:3, 2:3, 3:2, 3:1, 4:1 as shown in **Table 2**.

Evaluation of Ketoprofen Drug Loaded Pellets:

Drug Entrapment Efficiency: Drug loaded pellets theoretically containing 10 mg of the drug was weighed and transferred into a 10 ml centrifuge tube. The volume was adjusted to 10 ml by ethanol. This solution was kept on an ultrasound bath sonicator for 30 min. After this, the solution was filtered, and it was further diluted to a certain linearity range by adding distilled water. It was then estimated for ketoprofen content in a UV-Visible spectrophotometer at 258 nm against an appropriate blank [14].

Drug Entrapment Efficiency (%) = Experiment drug content in the formulation × 100 / Initial drug content in the formulation

***In-vitro* Drug Release Study:** The USP Type-II (Paddle type) *in-vitro* dissolution test apparatus (Lab India DS 8000) was used with 900 ml of pH 1.2(0.1N HCl) *i.e.* simulated gastric fluid without enzyme, as dissolution medium for first 2 h followed by in pH 6.8 phosphate buffer (simulated intestinal fluid without enzyme) for the next 3 h and finally at pH 7.4 phosphate buffer (simulated colonic fluid without enzyme) for up to 8 h maintain at 50 rpm paddle speed and 37 ± 0.5 °C temperature during the study. At regular intervals of time, an aliquot of 5 ml sample was withdrawn for evaluation and replaced by fresh dissolution medium to maintain sink condition. Samples were filtered through a 45 µm membrane filter and the filtrates were analyzed after suitable dilutions. Further dilutions of the sample were done to obtain a concentration inside the linearity range of the standards curves previously prepared and the assays were done using the UV-Visible spectro-photometer (Shimadzu UV-1800, Kyoto, Japan) at 258 nm. The concentrations of the drug were analyzed from the standard calibration curve and the percentage cumulative drug release was calculated [15, 16].

Drug Release Kinetics: To investigate the mechanism of drug release from the prepared pellets, the drug release data were fitted into first-order, zero-order models, Higuchi and Korsmeyer-Peppas models [17, 18].

Scanning Electron Microscopy: Surface topography of the pellets was examined for the optimized formulation batch both before and after dissolution using scanning electron microscopy. Samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were taken at an excitation voltage of 10 KV and at 400X magnification using Gemini SEM 300 [19].

Statistical Optimization: The data were expressed as mean ± SEM (standard error of the mean). Statistical differences between groups were analyzed using two-way Analysis of Variance (ANOVA) followed by Bonferroni post hoc test using GraphPad Prism 5.0 software. The Analysis of Variance was done using the Graph Pad Prism and p values< 0.05 were considered statistically significant.

RESULTS AND DISCUSSION:

Drug-Polymer Physical Compatibility Studies: Drug-polymer physical compatibility studies were performed for pure drug and when combined with excipients. The results were shown in **Fig. 1** and **2**. FTIR studies revealed that there is no change in the nature of the position of characteristic peaks of drug and excipients used to prepare the formulation bathes; hence it can be concluded that there is no interaction between drug and excipients.

Differential Scanning Calorimetry: Differential scanning calorimetric analysis of the Ketoprofen is showed in **Fig. 3**, and the drug-polymer physical mixture in **Fig. 4**. The thermograph of Ketoprofen showed a sharp melting point at 101.63, whereas in the thermograph of the drug-polymer physical mixture, the peak was observed at 99.69. It is confirmed that there was no major chemical interaction between the drug and the polymers except this small shift melting point indicating a mild physical interaction.

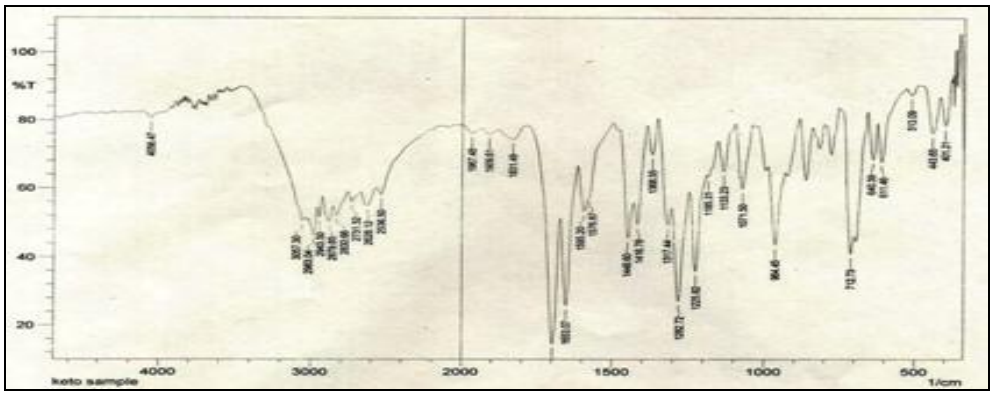

FIG. 1: FTIR SPECTRUM OF KETOPROFEN

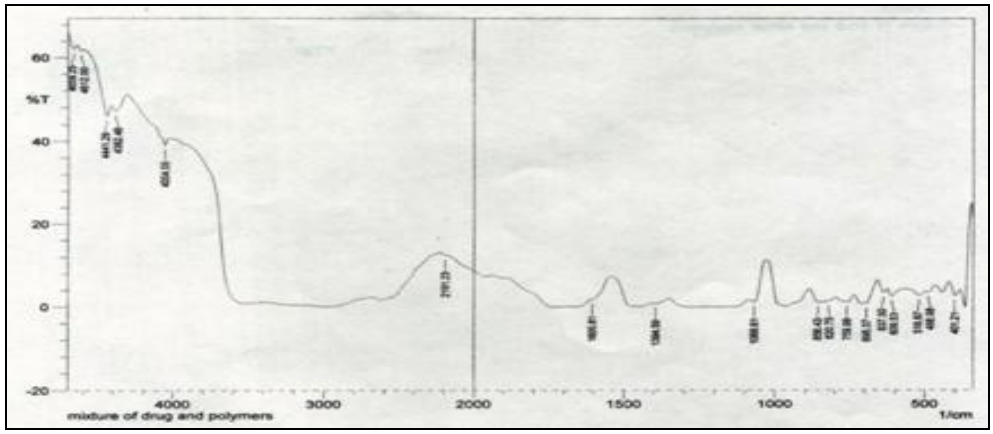

FIG. 2: FT-IR SPECTRUM OF DRUG POLYMER PHYSICAL MIXTURE

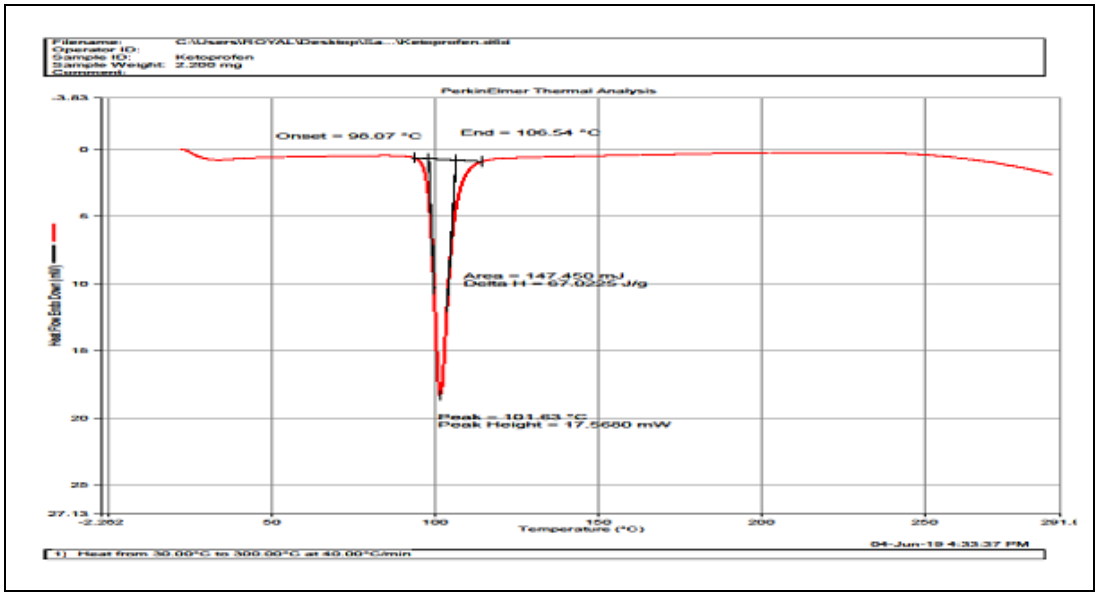

FIG. 3: DSC THERMOGRAPH OF KETOPROFEN

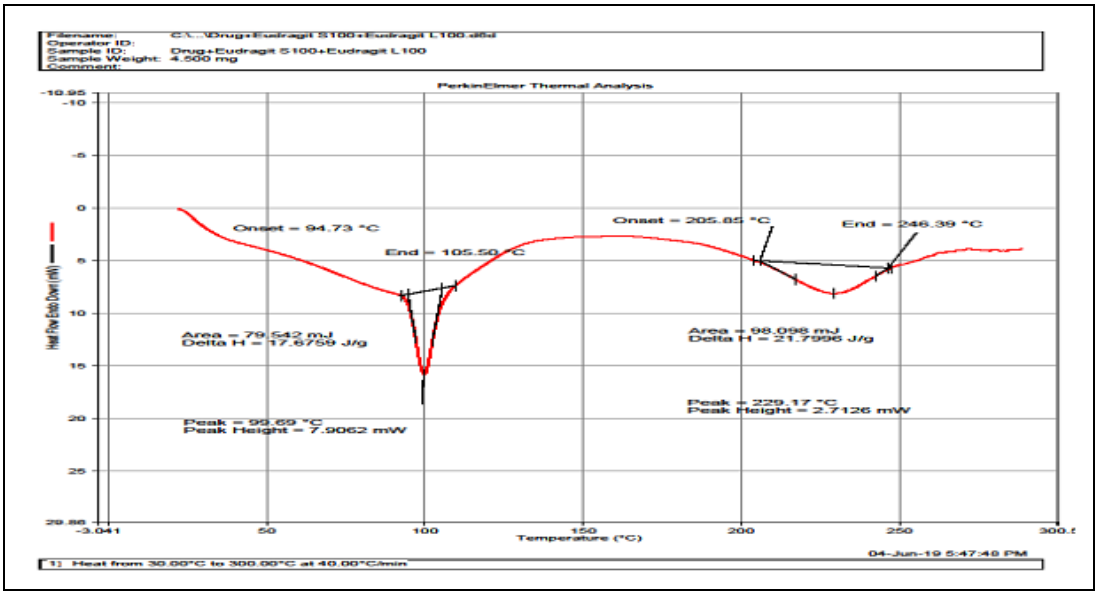

FIG. 4: DSC THERMOGRAPH OF DRUG-POLYMER PHYSICAL MIXTURE

Scanning Electron Microscopy: Scanning electron microscope photomicrographs of the drug-loaded pellets were taken before and after dissolution. SEM photographs of pellets **Fig. 5**

showed a smooth surface but after dissolution in pH 7.4 (SCF) medium **Fig. 6**, rough cakes appeared on the surface of the pellets, which might be due to degradation of Eudragit RS 100 and Eudragit L 100 polymer as it dissolved at higher pH. No polymeric film was seen on the surface of the pellet immersed in the dissolution medium (SCF).

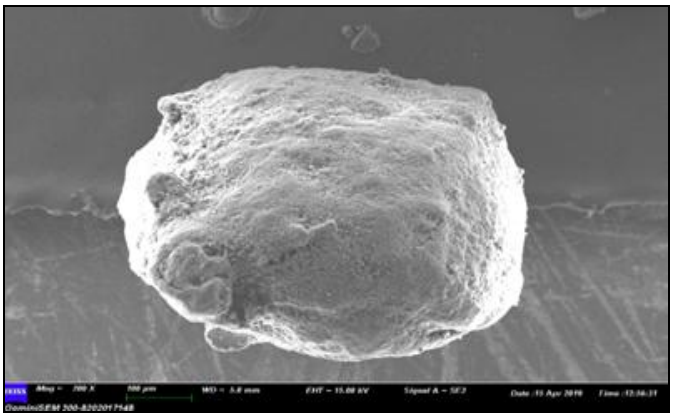

FIG. 5: SURFACE TOPOGRAPHY OF OPTIMIZED FORMULATION BEFORE DISSOLUTION USING SEM

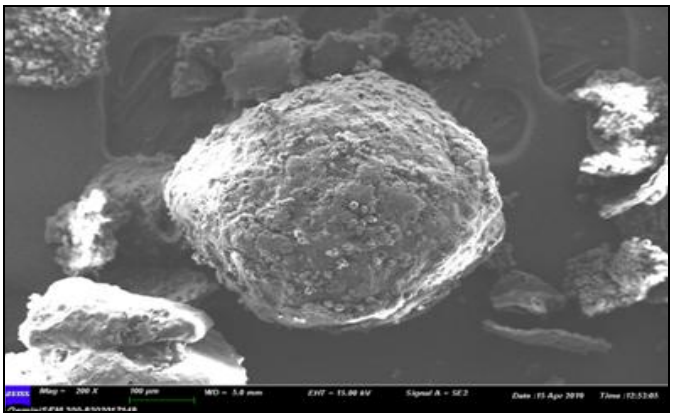

FIG. 6: SURFACE TOPOGRAPHY OF OPTIMIZED FORMULATION AFTER DISSOLUTION USING SEM

Drug Entrapment Efficiency: The drug entrapment efficiency of the coated drug-loaded multiparticulates were within the vary of 76.94 to 95.11% as shown in **Table 3**.

TABLE 3: DRUG ENTRAPMENT EFFICIENCY

Formulation code	Drug loading efficiency %
F_1	95.11%
F_2	85.25%
F_3	80.94%
F_4	94.62%
F_5	85.92%
F_6	81.98%
F_7	92.24%
F_8	82.79%
F_9	76.94%
F_{10}	94.35%
F_{11}	85.59%
F_{12}	77.70%
F_{13}	94.76%
F_{14}	86.06%
F_{15}	77.17%
F_{16}	95.08%
F_{17}	84.87%
F_{18}	78.54%
F_{19}	94.32%
F_{20}	85.11%
F_{21}	77.03%

These values prove the duplicability and simplicity of the powder layering technique. With an increase in the binder solution quantity or the percentage of binding agent used in the solution, there was an increase in the drug loading efficiency, however to a certain limit. A higher quantity of binding agent concentration within the binder solution or excess amount of binder solution can lead to increasing agglomeration of individual pellets into lumps. The drying of drug-loaded pellets is another vital issue; vary of time and temperature while drying can cause the powder drug to lose out from the core seeds. Minimum amount of wetting is required for the adherence of the drug particles over the surface of non-pareil seeds by forming liquid bridges.

***In-vitro* Drug Release Study:** Significant amount of drug released at target site was experimentally observed in case of optimized formulation (F15), which contained Eudragit S 100 and Eudragit L 100 in the ratio of 3:2 ratios at 20% TWG. Optimized formulation also showed minimum premature drug release of 14.32%. Eudragit S100: Eudragit L100 in the other ratios showed high drug release prematurely. *In-vitro* drug release data for formulation (F1-F11) showed in **Table 4** and for formulation, F12-F21 sowed in **Table 5**.

TABLE 4: COMPARATIVE *IN-VITRO* DRUG RELEASE STUDY OF VARIOUS FORMULATION BATCHES OF COATED KETOPROFEN DRUG LOADED PELLETS (F1-F11)

S. no.	pH	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	1.2	2	5.6	3.4	2.8	6.6	4.8	3.9	5.3	5.4	4.8	2.1	1.6
2	6.8	4	54.2	52.2	50.0	21.3	19.9	19.3	19.6	19.3	18.4	26.3	23.9
3	6.8	6	85.08	82.01	75.2	24.5	23.1	22.4	39.1	38.6	38.2	71.1	68.6
4	7.4	8				74.02	71.45	67.18	69.58	68.33	67.57	86.31	84.42
5	7.4	10				97.14	95.08	93.75	93.93	93.53	92.77	98.70	95.56

TABLE 5: COMPARATIVE *IN-VITRO* DRUG RELEASE STUDY OF VARIOUS FORMULATION BATCHES OF COATED KETOPROFEN DRUG LOADED PELLETS (F12-F21)

S. no.	pH	Time	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
1	1.2	2	0.9	4.14	3.42	2.69	9.88	8.44	6.64	8.62	8.08	7.36
2	6.8	4	23.5	21.03	17.57	14.32	28.10	26.27	23.55	26.72	25.78	24.15
3	6.8	6	66.3	56.25	52.93	47.37	65.99	56.77	49.46	58.73	57.29	55.67
4	7.4	8	81.26	81.19	77.11	73.01	84.56	79.42	73.22	82.39	81.08	78.95
5	7.4	10	93.51	98.10	91.39	87.14	97.57	93.15	87.07	94.53	93.33	91.70

Study of Drug Release Kinetics of Optimized Formulation Batch (F_{15}): The amount of Ketoprofen drug-loaded pellets released at 10 h from the optimized formulations was found to be 87.14%. The drug release data of all formulations were fitted to various popular drug release kinetic models. Various statistical parameters were determined in order to find the best suited kinetic model. The coefficient of determination (R^2) values of the Zero-order release model (0.9486) for the optimized batch was found to be significantly greater than R^2 values of the first-order drug release model (0.8915). The release exponent obtained from the Korsmeyer-Peppas model was found to have a value near 1, which further confirms that the release order was towards the zero-order kinetic model. Hence, drug release followed zero-order kinetics for optimized formulation (F15). The data is depicted in **Table 4**.

TABLE 4: ZERO ORDER, FIRST ORDER, HIGUCHI AND KORSMEYER-PEPPAS RELEASE KINETICS DATA OF DIFFERENT FORMULATION BATCH (F_{15})

Zero Order		First Order		Higuchi Method		Korsmeyer – Peppas	
Time (h)	Q% Drug Release	Time (h)	Log Q %Remaining To be Released	Sq. Rt of Time	Q % Drug Release	Log Time	Log Q % Drug Release
0.5	0.36	0.5	1.99844308	0.707107	0.36	-0.69315	-5.48916
1.0	1.61	1.0	1.99294069	1	1.61	0	-3.99128
2.0	2.69	2.0	1.98813591	1.414214	2.69	0.693147	-3.47797
2.5	7.25	2.5	1.96732865	1.581139	7.25	0.916291	-2.48651
3.0	15.86	3.0	1.92502337	1.732051	15.86	1.098612	-1.70371
4.0	16.32	4.0	1.9226263	2	16.32	1.386294	-1.67512
5.0	18.87	5.0	1.90920636	2.236068	18.87	1.609438	-1.52994
6.0	47.37	6.0	1.72123337	2.44949	47.37	1.791759	-0.60952
7.0	60.90	7.0	1.59217676	2.645751	60.90	1.94591	-0.35828
8.0	73.01	8.0	1.43120288	2.828427	73.01	2.079442	-0.17691
9.0	80.55	9.0	1.2889196	3	80.55	2.197225	-0.07863
10.0	87.14	10.0	1.10924096	3.162278	87.14	2.302585	-0.05543

TABLE 5: STATISTICAL ANALYSIS OF OPTIMIZED FORMULATION USING VARIOUS RELEASE KINETICS MODELS (F15)

Statistical parameter	Zero-order	First-order	Korsmeyer – Peppas	Higuchi Model
R^2	0.948	0.894	0.921	0.92
Regression equation	Y=10.18x -14.91	Y=-0.092x +2.182	Y=1.918-0.934	Y=39.05-46.23
Slope, m *release exponent	10.18	-0.092	0.934 *	39.05

CONCLUSION: Powder layering technique is an easy and persistent technique for the preparation of drug-loaded pellet sand proper and effective coating can be easily achieved over these drug-loaded pellets to obtain the coated multiparticulate systems. Eudragit S100 and Eudragit L100, being inert and pH-dependent polymers, were found to be an effective polymer for preparing targeted drug delivery systems intended for the colon. FT-IR and DSC studies have also proved that there was no drug-polymer interaction.

The scanning electron microscopic photographs of uncoated drug-loaded pellets were showing rough surfaces, indicating the adherence of drug particles which upon coating became smooth and crystalline.

There was no premature drug release before specified target site and a significant amount of drug released at a target site in case of an optimized formulation containing Eudragit S 100 and Eudragit L 100 in the ratio of 3:2 ratio at 20% coating level.

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CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Philip AK, Dabas S and Pathak K: Optimized prodrug approach: A means for achieving enhanced anti-inflammatory potentialin experimentally induced colitis. J Drug Target 2009; 17: 235-41.
2. Seth A, Jack EB and Vivek SD. Colon targeted oral drug delivery systems: Design Trends and Approaches 2015; 16(40): 731-41.
3. Dasankoppa FS, Patwa S, Sholapur H and Arunkumar GR: Formulation and characterization of colon specific drug delivery system of prednisolone. Saudi J Health Sci 2012; 1: 143-50.
4. Michele GI, Natalia V, Marcelo DD and Humberlo GF: Physical characterization of multiparticulate systems. Braz J Pharm Sci 2017; 53(4). Doi: 10.1590/s2175-97902017000400216
5. Kawashima Y, Okumura M and Takenaka H: Spherical crystallization: direct spherical agglomeration of Salicylic acid crystals during crystallization. Science 1982; 216(4): 1127-28.
6. Ogura Y, Bonen DK and Inohara N: A frame shift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001; 411: 603-06.
7. Caroline C, Jue W and Card T: The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014; 6: 71-80.
8. Patrono C and Rocca B: Nonsteroidal anti-inflammatory drugs: Past, present and future. Pharmacological Research 2009; 59: 285-89.
9. Brooks P: Use and benefits of nonsteroidal anti-inflammatory drugs. The American Journal of Medicine 1998; 104: 9S-13S.
10. Moumita D: Evaluation of polymers for compression coating of 5-amino salicylic acid matrix tablet of colon targeting. International Journal of Pharmacy and Pharmaceutical Sciences 2013; 3: 122-25.
11. Chunming SU and Donald LS: *In-situ* infrared speciation of adsorbed carbonate on aluminum and iron oxides. Clays Clay Miner 1997; 45: 814-25.
12. Hussain A and Khan GM: Development of a novel ketoprofen transdermal patch: Effect of almond oil as penetration enhancers on *in-vitro* and *ex-vivo* penetration of ketoprofen through rabbit skin. Pak J Pharm Sci 2012; 25(1): 227-32.
13. Subhabrota M: Pectin based multiparticulate formulation of Ketoprofen for bacterial enzyme dependent drug release in colon. Trends Biomater. Artif Organs 2011; 25(4): 133-43.
14. Hina R, Nazar MR, Asif M, Farooq A, Rai MS and Zermina R: Development and *in-vitro* characterization of 5-flurouracil loaded, colon-targeted drug delivery system. Tropical Journal of Pharmaceutical Research 2018; 17(2): 105-04.
15. Anchal, Ashu M, Debaprasad G and Jagannath S: Challenges in development of colon drug delivery system with respect to dissolution studies. WJPP 2019; 8(6): 1465-91.
16. Subhashish D: Formulation and evaluation of floatable in situgel as a carrier for stomach specific drug delivery of metoclopramide HCl. Int J Pharm Res 2011; 1: 53-64.
17. Mittal A, Sara UVS, Ali A and Mohammed A: Design, Development, physicochemical, *in-vitro* and *in-vivo* evaluation of monolithic matrix type transdermal patches containing nitrendipine. Pharmaceutical Development and Technology 2009; 14(4): 422-34.
18. Mittal A, Sara UVS and Ali A: Formulation and evaluation of monolithic polymer fims for transdermal delivery of nitrendipine. Acta Pharm 2009; 59(4): 383-93.
19. Kala D and Nair CRS: Formulation and *in-vitro* evaluation of budesonide microspheres for colon targeting. Int J Pharm Sci Res 2016; 7(2): 697-02.

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