RESEARCH ARTICLE

Formulation and *in vitro/in vivo* Evaluation of Control Targeted-release Budesonide Multi-unit Pellet Tablets for Colon Targeting

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Abstract

Aim: The aim is to study the formulation and evaluation of budesonide multi-unit pellet tablets and is designed to release in both delayed and control release fashion with the objective of less *in vitro* and *in vivo* variability. **Materials and Methods:** Budesonide is class-II drug and insoluble in water. The major concerns with the budesonide are its poor solubility which results into poor drug release profiles and poor bioavailability after oral administration. Control release of drug and targeting to colon is another challenging, thereby reducing side effect, frequency of dose, and improved oral bioavailability and decreasing *in vitro* and *in vivo* variability. Micronization using high-pressure homonization milling with polysorbate 80 was chosen for improving solubility. Multi-unit pellet tablets technology was chosen for this purpose, and the optimal formulation was manufactured by suspension layering and solution layering methods in fluidized bed processor (FBP). The prepared MUPS tablets were tested for *in vitro*/*in vivo* performance. **Results and Discussions:** The *in vitro* drug release of the prepared formulation compared with marketed product showed similarity f2 = 65.18 in Ph 7.5 phosphate buffer, f2 = 70.13 in Ph 7.5 phosphate buffer with MCE, f2 = 65.05 in Ph 7.2 phosphate buffer, f2 = 60.30 in Ph 7.2 phosphate buffer without MCE to the marketed product, f2 = 53.34 in Ph 6.8 phosphate buffer, and f2 = 52.51 in Ph 6.8 phosphate buffer without surfactant. In pH 4.5, pH 6.0, and pH 6.5 media optimized formulation and marketed products, significant release was not observed. The pharmacokinetic study showed no significant difference ($P > 0.05$) in Cmax, AUC0-24 between the test and reference formulations observed, whereas subject variability observed more in reference formulation compared to test formulation. **Conclusion:** The obtained results suggested that micronization, MUPS technology with control release coating, and pH-dependent coating might be an efficacious approach for control release and targeted release of budesonide to colon with less *in vitro* and *in vivo* variability.

Key words: Budesonide, control release, ethyl cellulose, MUPS Technology, targeted release

INTRODUCTION

Ulcerative colitis (UC) is the chronic relapsing multifactorial gastrointestinal inflammatory bowel disease, which is characterized by bloody or mucus diarrhea, tenesmus, bowel distension, an anemia. The annual incidence of UC in Asia, North America, and Europe was found to be 6.3, 19.2, and 24.3 per 100,000 person-years.[1] The major challenge in the treatment of UC is appropriate local targeting and drug-related side-effects. Budesonide is an anti-inflammatory substance, it is synthetic corticosteroid, and budesonide is designated chemically as (RS)-11β, 16α, 17,21 tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Uceris is a new formulation of budesonide with a proposed indication of induction of remission in adult patients with mild-to-moderate active UC.[2] Currently, there are various approved

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budesonide formulations available on the market for other indications including inhalation, nasal, and oral capsule formulations. Entocort EC capsule is the oral formulation of budesonide available on the market with an indication for Crohn's disease. UCERIS is designed as matrix tablets to release budesonide in both delayed and extended release fashion to target the delivery of budesonide at the colon.[3] However, this formulation showing significant *in vitro* and *in vivo* variability[4] was observed, and hence alternative study attempted to improve variability.

Modified release tablets with sustained drug release behaviors could maintain their therapeutically effective concentrations in systemic circulation for prolonged periods of time, which decreases the number of daily administrations, minimizing local and systemic side effects. Thus, it improves the patient compliance with prescribed dosage regimens.[5] Multiparticular formulation for colon delivery of drugs with more uniform *in vivo* dissolution performance compared to single-unit dosage forms.[6] Single-unit formulations contain the active ingredient within the single tablet or capsule, whereas multiple-unit dosage forms comprise a number of discrete particles that are combined into one dosage unit. Other advantages of this divided dose include ease of adjustment of the strength and administration of incompatible drugs in a single dosage unit by separating them in different multiparticulates and different drug-release rates to obtain the desired overall release profile. MUPS technology offering increased bioavailability and improved pharmacological properties, including sustained release, enteric-coated pellets containing different drugs, and subsequently tabulated, can be used to protect the API from gastric media. Compressing pellets reduce the esophageal residence time, compared with capsules, and improves physicochemical stability. Further, compared with other delivery systems, MUPS formulations offer a lower risk of local irritation and toxicity, reduced dose dumping, minimal plasma concentration fluctuations, and the ability to administer high potency products. More reproducible pharmacokinetic behavior and lower intra-/inter-subject variability compared with conventional formulations have also been reported.

There is very limited research which was done on budesonide 9 mg pellets formulation which is intended for treatment of UC, most of the work found as matrix tablets.[7,8] To take the advantage of the pellets as well as to meet the requirement of treatment of UC, this study aimed to develop it's in both delayed and extended release fashion to target the delivery of budesonide pellets to the colon using MUPS system. A MUPS consists of (i) drug-loading control-release polymer matrix pellets, (ii) enteric coating consists of pH-dependent polymers, and (iii) overcoating layer which consists of highly bonding polymer. The MUPS tablets were prepared and assessed for their *in vitro* behavior and *in vivo* performance.

MATERIALS AND METHODS

Materials

UCERIS (budesonide) 9 mg control release tablets were obtained from Santarus, Inc., San Diego, CA 92130, manufactured by Cosmo S.p.A., Milan, Italy. Budesonide drug substance was gifted by Hetero Drugs Ltd., Hyderabad, India. Ethyl cellulose aqueous dispersion (Aqua coat ECD-30) and Croscarmellose sodium (Ac-Di-Sol) was purchased from FMC Biopolymer 1301 Ogletown Road, Newark, DE 19711, USA. Suger sphears (#40/#60) Pharma-A-Spheres gifted by Hanns G. Werner GmbH + Co. KG, Germany. TEC gifted by Vertellus Performance Materials Inc. 2110 High PointRoad, Greensboro, N.C. Polysorbate 80 gifted by CrodaSingapore Pvt Ltd. 30 seraya Avenue, Singapore 627884. Methacrylic acid copolymer type A (Eudragit L100) and methacrylic acid copolymer type B (Eudragit S100) gifted by Evonik Industries AG Pharma polymers, Kirschenallee, 64293 Darmstad, Germany. Talc gifted by Luzenac Val Chisone SPA/IMERYS TALC Italy SpA, Sede Legalee Stabilimento: via Porte (To), Nazinalen 121-10060, Italy. Titanium dioxide gifted by Kronos International Inc, Peschstrass 5, D 51373, Leverkusen, Germany. Isopropyl alcohol gifted by Deepak Fertilizers & Petro chemicals corporation Ltd. Acetone gifted by Klucel gifted by Aqualon Hercules. Polyethylene glycol 6000 gifted by Clariant Chemicals (India) Ltd. Methylene chloride gifted by Gujarat Fluro Chemicals Ltd. Silicified Microcrystalline Cellulose (Prosolv HD90) gifted by JRS Pharma. Magnesium striate gifted by Peter Greven Nederland C.V Edison street,1,5928 Pg fvenlo, The Netherlands.

Methods

Preparation of budesonide 9 mg delayed and control release pellets

Budesonide is delayed and control-release pellets were composed of four parts, namely, nonpareils (sugar spheres), drug-polymer layer, enteric-coated layer, and overcoating layer successively. All the layers were prepared in a FBP [Table 1] by the suspension and solution layering methods. Formulation includes prepared micronized suspension of budesonide and then mixed this micronized suspension with control release polymer Aqua coat ECD-30 and loaded this suspension on sugar spheres after completion of drug-polymer layering, Eudragit enteric coated solution was prepared and coated on drug-loaded pellets, and finally, overcoating was given on the enteric coated pellets to prevent cracking of function layers after preparation of overcoated pellets pre-lubrication and lubrication was done followed by compression and film coating. The drug polymer loaded pellets should be dried for 2 h at 60°C, and enteric coated and overcoated pellets should dried for 30 min at 45°C and then weighted to calculate the weight gain when their temperature reached room temperature.

Drug polymer matrix layer

It includes preparation of micronized suspension of budesonide, polysorbate 80 was dissolved in purified water with continues stirring till clear solution was formed and then added the budesonide drug substance slowly to this solution and continued the stirring till homogenous suspension formed. Taken this suspension and homogenized using high-pressure homogenizer (make: Gea, panda) at pressure of 1500 bars for 60 min.

A bead size of 250–420 µm was selected for drug loading, as the drug is insoluble in water, and hence, we selected soluble core sugar spheres. The prepared budesonide dispersion was mixed with aqueous ethyl cellulose dispersion aquacoat ECD-30d, added plasticizer triethyl citrate under stirring, and continued the stirring throughout process. Selected core pellets were loaded in Fluid bed spray processor (Glatt 1.1) and coated these core pellets with drug-aqueous ethyl cellulose dispersion by using 1.5 mm nozzle, and parameters are compiled in Table 1. After completion of coating core, pellets were cured at 60°C for 2 h.

Preparation of enteric coated pellets

Isopropyl alcohol (80% of total solvent) was taken in container equipped with a propeller stirrer and taken remaining quantity of isopropyl alcohol (20% of total solvent) in another vessel equipped with homogenizer. Added the methacrylic acid copolymer type A (Eudragit L100), methacrylic acid copolymer type B (Eudragit S100) slowly to the isopropyl alcohol (80% of total solvent) while stirring. Increase the speed of stirrer if necessary. Continued stirring for 60 min and purified water was added under stirring, then it forms clear solution.

Added the talc, titanium dioxide, and triethyl citrate slowly to the isopropyl alcohol (20% of total solvent) under continuous homogenizing. Continued homogenization for 45 min or till smooth dispersion is obtained. Mixed the both solution and talc dispersion and stirred it for 15 min and kept the dispersion under constant agitation, at slow speed, during the entire process. Load the drug-loaded pellets in FBP (GATT) and coated these pellets with enteric coating using the parameter mentioned in Table 1.

Preparation of over coating pellets

PEG 6000 was added into isopropyl alcohol and methylchloride mixture under stirring, added Klucel LF slowly to the solution till to get clear solution, and added purified water to this solution slowly under stirring. The prepared solution was coated on enteric coated pellets using parameters compiled in Table 1.

The overcoated pellets were mixed with extragranular and lubricants and prepared final blend, and the final lubricated blend was compressed in tablets and coated final tablets with film coating materials [Table 2].

Differential scanning calorimetry (DSC)

DSC studies were carried out using DSC Q2000 V24.11 Build 124. Accurately weighed samples were placed on aluminum plate, sealed with aluminum lids, and heated at a constant rate of 10 °C/min, over a temperature range of 30–350°C.

Characterization of optimized pellets

Optimized pellets were evaluated by yield of pellets, angle of repose, friability, and particle size distribution. The yield of pellets was calculated by the following formula:

$$\text{Yield of pellets } (\%) = \frac{\text{Practical yield of pellets}}{\text{Theoretical yield of pellets}} \times 100\%$$

Friability of pellets was tested by a friabilator. 10 g of in-house pellets and 25 glass balls were mixed together to be centrifuged for 10 min at 30 rpm. The pellets were collected and weighted. As a result, the percentage of weight loss of the pellets was calculated.[9]

Drug release measurements and comparisons

In vitro drug release profiles for optimized formulation of budesonide MUPS tablets and corresponding reference product (Uceris 9 mg ER tablets) were performed using below media, and were tested in 500 ml of 0.1 N HCL (simulated gastric fluid) followed by the acetate and phosphate buffers of pH 4.5, pH 6.0, pH 6.5 pH 6.8, pH 7.2,

Table 1: Drug loading, enteric coating, and over coating process parameters.

Process parameter	Drug loading	Entering coating	Over coating
Coating type	Aqueous coating	Aqueous coating	Non-aqueous coating
Product temperature	42°C±5°C	42°C±5°C	35°C±5°C
Fluidization (CFM)	7–11	7–11	7–11
Atomization (Bar)	1–3	1–3	0.5–1.5
Spray rate (g/min)	10–20 g/min	10–20 g/min	10–20 g/min
Wurster (mm)	20	20	20

Table 2: Budesonide 9 mg controlled release MUPS tablets formula

Ingredient	Function	Qty mg/unit				
Core		BUD-I	BUD-II	BUD-III	BUD-IV	BUD-V
Suger spheres (#40/#60) Pharma-A-Spheres	Supporting core	180	180	180	180	180
Drug loading						
Budesonide	Active	9.00	9.00	9.00	9.00	9.00
Aqua coat ECD30D	Control release polymer	6.00	9.00	12.00	18.00	24.00
Klucel	Pore former	1.80	1.80	1.80	1.80	1.80
Triethyl citrate	Plasticizer	1.80	1.80	1.80	1.80	1.80
Polysorbate 80	Surfactant	5.00	5.00	5.00	5.00	5.00
Purified water	Solvent	30.00	30.00	30.00	30.00	30.00
Weight of control release pellets		203.60	206.60	209.60	215.60	221.60
Target release coating						
Methacrylic acid copolymer type A (Eudragit L100)	Enteric polymer	6.00	6.00	6.00	6.00	6.00
Methacrylic acid copolymer type B (Eudragit S100)	Enteric polymer	8.00	8.00	8.00	8.00	8.00
Talc	Antistatic agent	2.80	2.80	2.80	2.80	2.80
Titanium dioxide	Pacifier	5.00	5.00	5.00	5.00	5.00
Triethyl citrate	Plasticizer	1.40	1.40	1.40	1.40	1.40
Isopropyl alcohol	Solvent	110	110	110	110	110
Water	Solvent	10	10	10	10	10
Weight of pellets		226.80	229.80	232.80	238.80	244.80
Over coating						
Klucel	Binder	16.50	16.50	16.50	16.50	16.50
PEG 6000	Plasticizer	5.50	5.50	5.50	5.50	5.50
Isopropyl alcohol	Solvent	150	150	150	150	150
Acetone	Solvent	75	75	75	75	75
Water	Solvent	20	20	20	20	20
Weight of overcoated pellets		248.80	251.80	254.80	260.80	266.80
Silicified MCC	Diluent	255.20	252.20	249.20	243.20	237.20
PEG 6000	Plasticizer	60.00	60.00	60.00	60.00	60.00
Croscarmellose	Disintegrant	30.00	30.00	30.00	30.00	30.00
Magnesium stearate	Lubricant	6.00	6.00	6.00	6.00	6.00
Weight of MUPS core tablet		600.00	600.00	600.00	600.00	600.00
Film coating						
Opadry white	Film coating	18.000	18.000	18.000	18.000	18.000
Purified water	Solvent	qs	qs	qs	qs	qs
Weight of final MUPS tablet		618.00	618.00	618.00	618.00	618.00

and pH 7.5 using apparatus II (Paddle apparatus) in USP. In this study, we evaluated the similarity between in-house tablets and marketed capsule (UCERIS®) in all media with and without surfactant macrogol cetostearyl ether. As a parameter of similarity evaluation, the similarity factor (f2) plays a significant role in comparing the dissolution profiles. f2 (shown in the following formula[2]) is a logarithmic transformation of the sum-squared error of differences between the reference and the tested preparations over all time points.[4]

$$f_2 = 50 \times \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{1/2} \times 100\right\}$$

Log stands for logarithm based on 10. It is recommended that two dissolution profiles can be determined to be similar when f2 value exceeds 50.

Apparatus: USP apparatus 2 (paddle).

Acid stage: 2 h in 0.1 N HCl at 100 rpm (500 ml)

Buffer stage: Each of

1. 0.5% macrogol cetostearyl ether in pH 4.5 acetate buffer at 100 rpm
2. Without macrogol cetostearyl ether in pH 4.5 acetate buffer at 100 rpm
3. 0.5% macrogol cetostearyl ether in pH 6.0 phosphate buffer at 100 rpm
4. Without macrogol cetostearyl ether in pH 6.0 phosphate buffer at 100 rpm
5. 0.5% macrogol cetostearyl ether in pH 6.5 phosphate buffer at 100 rpm
6. Without macrogol cetostearyl ether in pH 6.5 phosphate buffer at 100 rpm
7. 0.5% macrogol cetostearyl ether in pH 6.8 phosphate buffer at 100 rpm
8. Without macrogol cetostearyl ether in pH 6.8 phosphate buffer at 100 rpm
9. 0.5% macrogol cetostearyl ether in pH 7.2 phosphate buffer at 100 rpm
10. Without macrogol cetostearyl ether in pH 7.2 phosphate buffer at 100 rpm
11. 0.5% macrogol cetostearyl ether in pH 7.5 phosphate buffer at 100 rpm
12. Without macrogol cetostearyl ether in pH 7.5 phosphate buffer at 100 rpm.
    - Volume: 1000 ml
    - Temperature: 37°C.

Determination of drug content and content uniformity of MUPS tablets

The drug content was determined by the method of HPLC. Agilent Phenomenex Kinetex C18 column (5 µm, 150 × 4.6 mm) was optimized in a column oven with the temperature maintained 40°C. The injection volume was 20 µL, the flow rate was 1.2 ml/min, and the UV detector wavelength was set at 254 nm.

For buffer, 3.17 g/l of sodium dihydrogen phosphate monohydrate in 1000 ml water was prepared, and adjust pH of solution to 3.2 ± 0.05 with 5% v/v dilute orthophosphoric acid solution.

Mobile phase was formed from buffer and acetonitrile in the ratio of 70:30% v/v.

Diluent was formed from water and methanol in the ratio of 50:50% v/v.

The contents of NLT 10 capsules were ground with a mortar and pestle into fine powders. Then, powders (equivalent to approximately 30 mg budesonide) were precisely weighed and transferred into a 100 ml volumetric flask. Add about 60 ml of methanol and sonicate for 30 min with intermediate shaking. Dilute to volume with methanol and mix. Centrifuge apportion of the solution at 5000 rpm for 10 min. Filter the solution through 0.45 um membrane filter and discard first few ml of the filtrate. Transfer 5 ml of prepared solution into 25 ml volumetric flask, dilute to volume with diluents, and mix to get sample solution for measurement of assay.

Release kinetics.

Kinetic studies were conducted for reference and optimizing formulations in Ph 7.2 phosphate buffer containing 0.5% surfactant as it is official media in US FDA site and hence selected this media for evaluation of kinetic models. It was inferred that there were three probable ways for drug release from the polymeric membrane to medium: (1) The drug is dispersed into the membrane, permeated through the consistent polymeric network, and then, redistributed in the polymeric framework and diffused to the medium, (2) the drug is dispersed to medium through tiny holes or cracks existing in the membrane, and (3) the coalition of the above two. Different mathematical models were applied to study the *in vitro* dissolution behaviors of the pellets, including zero-order model,[10] first-order model,[11] Higuchi model,[12] Ritger–Peppas model,[13] Hixson–Crowell model, Baker–Lonsdale model,[14] and Weibull model.[15] Regression analysis was conducted, and then, the best fits were calculated based on correlation coefficient as r.[16]

Of the models above, Ritger–Peppas model[13] was applied for further analyses of drug release mechanism. Equation of Ritger–Peppas model was shown in the below formula. Qt denoted the accumulated release at time (t), kR expressed the constant rate of drug release, while n was an important parameter indicating the release mechanism. If $n \leq 0.45$, the mechanism was Fickian diffusional. If $0.45 <$"n" < 0.89, the release mechanism was non-Fickian dispersion including Fickian-diffusional and relaxation. If $n \geq 0.89$, the relaxation played a sole role in drug release.

$$\ln Qt = n \ln t + kR$$

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (Cmax), time to attain Cmax, i.e., Tmax and t1/2values, area under plasma concentration-time curve from zero to the last sampling time (AUC0-t), and area under plasma concentration-time curve from zero to infinity (AUC0-∞).

Stability study

The optimized budesonide tablets and UCERIS tablets were placed into the condition of 40°C/75% RH for 1 month. Samples were analyzed for the dissolution profiles, contents, and related substances.

RESULTS AND DISCUSSION

DSC

The DSC measurements were performed for budesonide API, budesonide MUPS tablets, and placebo of budesonide MUPS tablets to study drug excipient interaction on a DSC with a thermal analyzer. The DSC thermogram is shown in Figures 1-3.

The DSC of budesonide [Figure 1] showed sharp endothermic peak at 259.39°C which corresponding to melting point of drug, DSC thermogram of MUPS tablets placebo showed sharp peak at 189.25°C and DSC thermogram of MUPS tablets which contain micronized budesonide and polysorbate 80 coated pellets showed two peaks at 57.25°C and 189.25°C indicating that there is some interaction between surfactant and drug during high-pressure homogenization, which is required for the improvement of solubility of budesonide in budesonide-polysorbate 80 solid dispersion. No melting peak of drug at 259.39°C appeared in this thermogram indicating the complete dispersion of the drug in the polysorbate 80 due to phase transition.

Physical characterization of budesonide pellets and MUPS tablets

The optimal budesonide pellets were achieved with 91.5 ± 0.2% of yield and 0.05 ± 0.02% of friability. The optimizes budesonide MUPS tablets were achieved 85.9 ± 2% of yield and 0.07 ± 0.02% of friability.

Effect of polymer concentration on budesonide release

In vitro dissolution profile of budesonide MUPS tablets and innovator product are summarized in Table 3 having different concentration of control release polymer in 7.2 phosphate buffer with 0.5% macrogol cetostearyl ether.

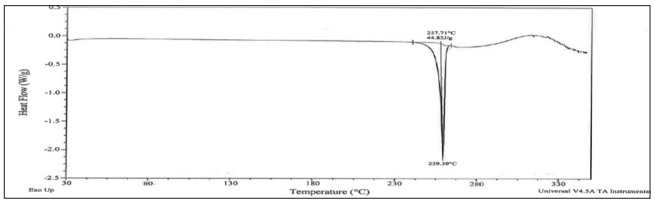

Figure 1: Budesonide API differential scanning calorimetry spectrum

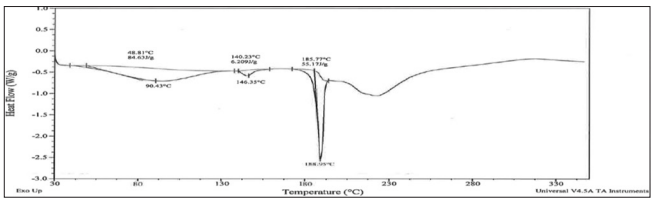

Figure 2: Budesonide MUPS tablets placebo differential scanning calorimetry spectrum

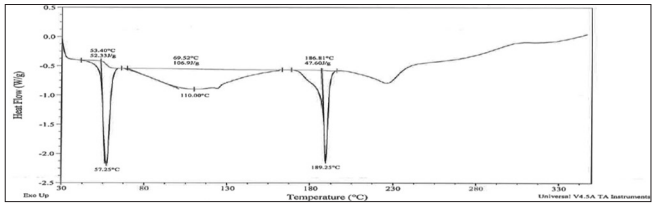

Figure 3: Budesonide MUPS tablets placebo differential scanning calorimetry spectrum

Table 3: Comparative dissolution profiles of various formulation BUD-I, BUD-II, BUD-III, BUD-IV, and BUD –IV in 7.2 phosphate buffer with 0.5% macrogol cetostearyl ether, at 100 RPM.

Time (h)	Cumulative % drug release					
	UCERIS 9 mg tablets	Budesonide 9 mg MUPS tablets				
		BUD-1	BUD-II	BUD-III	BUD-IV	BUD-V
Acid stage: 2 h	0	4	4	0	0	0
Buffer stage: 1 h	4	65	49	20	8	2
2 h	22	83	73	45	15	27
3 h	43	92	87	62	37	38
4 h	65	95	93	80	73	62
6 h	94	98	95	93	101	85
8 h	96	100	95	100	101	91
10 h	96	101	96	101	101	91

BUD-I and BUD-II formulations show faster release profiles, these two formulations release more than 49% within 1 h, BUD-III formulation is releasing faster than reference product, whereas BUD-V formulation releasing slower than reference product, and hence, based on above *in vitro* dissolution profile data, BUD-IV formulation was selected for further evaluation. Finally, it is conclude that as the concentration of polymer increases, dissolution rate was decreasing, we found that optimum concentration of polymer in formulation is 18 mg of Aqua coat ECD30D per tablet [Table 3 and Figure 4].

Effect of budesonide release in different media which covers entire GIT track

The optimized formula and UCERIS reference tablets dissolution profiles were checked in different media which covers throughout GIT track, as the drug is controlled colon targeted, and hence, we checked dissolution profiles in different media which covers throughout GIT.

The dissolution profile of optimized formulation in pH 4.5 acetate buffer, pH 6.0, pH 6.5, pH 6.8, pH 7.2, and pH 7.5 phosphate buffers with and without surfactant was summarized in Tables 4 and 5, respectively. From below results, it was observed that up to pH 6.5 there is no significant release was observed, in pH 6.8 phosphate buffer, the drug was released less compared to pH 7.2 and pH 7.5 medias. The drug was released completely in pH 7.2 and pH 7.5 phosphate buffer with surfactant, from above data lag time observed before releasing the drug at targeted site [Figures 5-10].

Budesonide MUPS tablets content uniformity

Content uniformity is one of the commonly occurred problems in MUPS tablets. We checked the content uniformity of

Table 4: Dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets (BUD-IV) in different medias with surfactant

Time (h)	pH 4.5 acetate buffer		pH 6.0 phosphate buffer		pH 6.5 phosphate buffer		pH 6.8 phosphate buffer		pH 7.2 phosphate buffer		pH 7.5 phosphate buffer	
	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV
Acid 2	0	0	0	0	0	0	0	0	0	0	0	0
Buffer: 1	0	0	0	0	0	0	0	0	2	3	3	6
2 h	0	0	0	0	0	0	0	5	13	14	9	11
3 h	0	0	0	0	0	0	16	21	27	31	19	20
4 h	0	0	0	0	0	0	29	40	42	47	29	35
6 h	0	0	0	0	0	1	64	74	76	86	53	61
8 h	0	0	2	2	3	4	82	90	85	85	70	76
10 h	0	0	7	5	5	14	86	94	88	89	78	82
F2		-		-		-		53		65		65

Table 5: Dissolution profiles of UCERIS 9 mg tablets and Budesonide 9 mg MUPS tablets (BUD-IV) in different media with surfactant

Time (h)	Ph 4.5 acetate buffer		Ph 6.0 phosphate buffer		Ph 6.5 phosphate buffer		Ph 6.8 phosphate buffer		Ph 7.2 phosphate buffer		Ph 7.5 phosphate buffer	
	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV	UCERIS	BUD-IV
Acid 2	0	0	0	0	0	0	0	0	0	0	0	0
Buffer: 1	0	0	0	0	0	0	0	0	4	8	3	4
2 h	0	0	0	0	0	0	7	6	22	15	10	12
3 h	0	0	0	0	1	0	21	21	43	37	19	22
4 h	0	0	1	0	3	0	35	35	65	73	31	35
6 h	0	0	1	0	11	3	54	69	94	101	61	68
8 h	2	0	2	4	32	11	86	86	96	101	93	96
10 h	7	0	6	9	68	65	94	97	96	101	100	100
F2		-		-		-		53		60		70

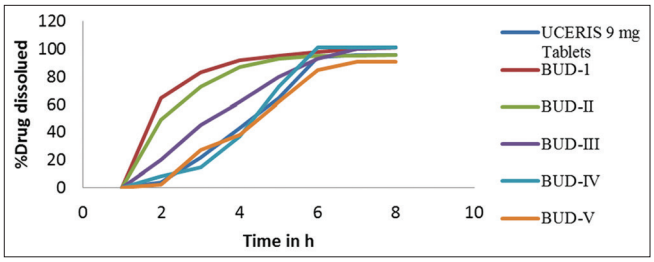

Figure 4: Comparative dissolution profile in 0.5% macrogol cetostearyl ether in pH 7.2 acetate buffer at 100 rpm of BUD-I, BUD-II, BUD-III, BUD-IV, and BUD-V

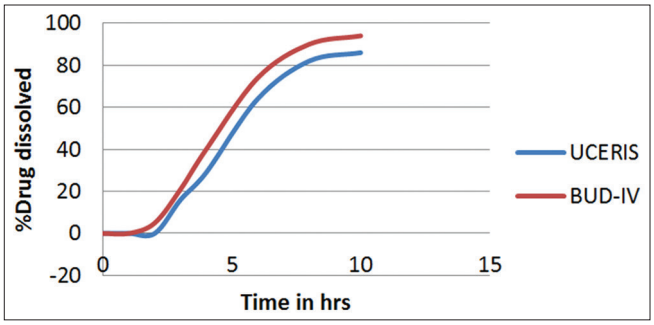

Figure 5: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 6.8 phosphate buffer

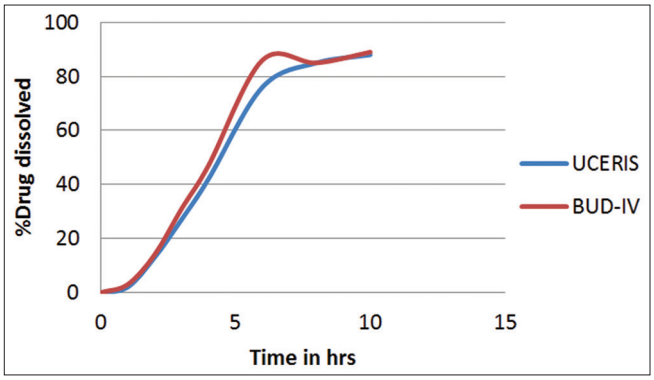

Figure 6: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 7.2 phosphate buffer

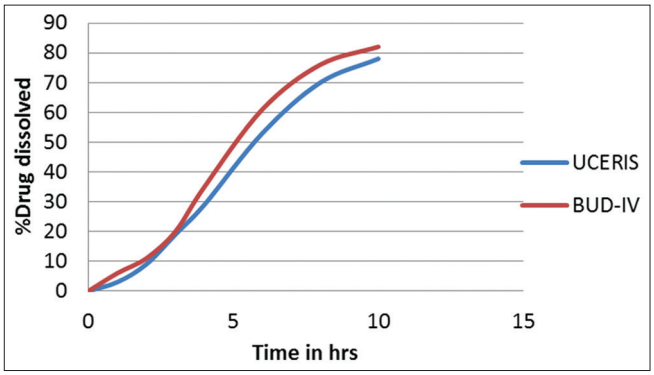

Figure 7: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 7.5 phosphate buffer

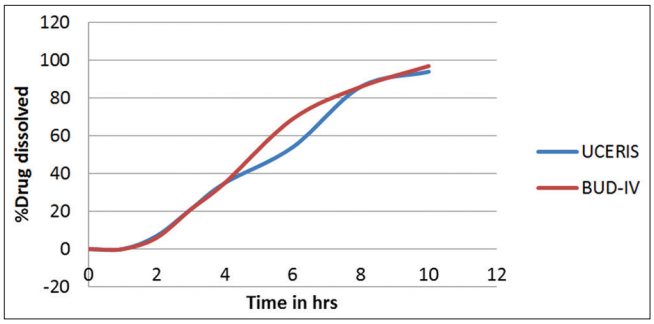

Figure 8: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 6.8 phosphate buffer with surfactant

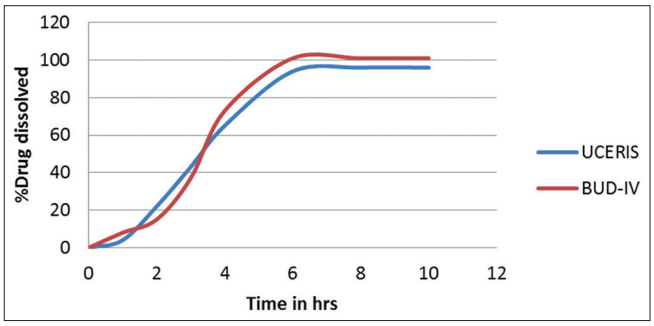

Figure 9: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 7.2 phosphate buffer with surfactant

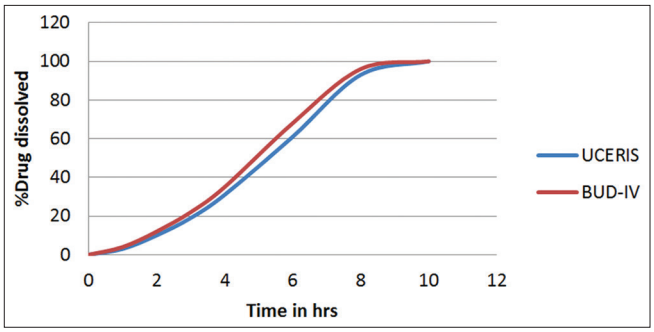

Figure 10: Comparative dissolution profiles of UCERIS 9 mg tablets and budesonide 9 mg MUPS tablets in 7.2 phosphate buffer with surfactant

optimized formula and results are summarized in Table 6. All tablets are well within the USP limits 90–110% w/w.[17] The lowest value observed is 94.6% and highest value observed is 99.6%. From below results, it was conclude that tablets were having good uniformity.

The mechanism of drug release

The different kinetic models were applied to marketed reference and optimized formulations in Ph 7.2 phosphate buffer containing 0.5% surfactant as it is official media in the US FDA site , dissolution profiles showed in Table 7 and hence selected this media for evaluation of kinetic models and the results were shown in Table 8. It was observed that zero-order

model and Hixson–Crowell model were fitted for Uceris®, and optimized formula is consistent with the marketed. The "n" of Ritger–Peppas model was 1.781 of UCERIS®, while the "n" was 1.514 of optimized formula. As a consequence, we can draw the conclusion that relaxation plays a key role in the drug release of UCERIS® and in-house product.

Pharmacokinetic parameters comparison for reference product and optimized MUPS formulation

The budesonide plasma concentrations in healthy humans voluntaries treated with optimized formulation (BUD -IV) were no significantly difference between those treated with reference, but, whereas, subject variability was found more in reference formulation compared with optimized in house formulation. Plasma pharmacokinetic parameters of budesonide after oral administration of the formulation to humans are presented in Table 9.

Results of stability study

The stability studies were conducted on optimized formulation at 40°C/75% RH, 3 months, and the results were summarized in Table 10. The dissolution profiles, assay, and related substances were analyzed up to 3 months, and it showed that there is no significant difference between initial samples and 1 month, 2 months, and 3 months 40°C/75% RH samples, and the release profile, assay, and related substances indicate stability of the tablets according to accelerated stability of the ICH guidelines up to 3 months.

CONCLUSION

In the present study, budesonide targeted and controlled MUPS tablets were successfully prepared by using Eudargit polymers and insoluble polymer ethyl cellulose. Based on *in vitro* drug release profiles of formulation BUD4, it was clearly evident that drug was released in delayed and controlled manner, and *in vitro* and *in vivo* unit-to-unit variability of MUPS in-house optimized tablets is less compared to reference matrix tablets (UCERIS 9 mg tablets),

Table 6: Content uniformity of MUPS tablets

S. No	Drug content
1	94.9
2	97.4
3	99.6
4	97.4
5	96.1
6	95.6
7	97.3
8	99
9	94.6
10	97.0
Mean	96.9
RSD (%)	1.65
Min	94.6
Max	99.6

Table 7: Dissolution Profile in 0.5% Macrogol Cetostearyl Ether in pH 7.2 phosphate buffer at 100 rpm

Time (h)	Cumulative % drug release (%RSD)	
	UCERIS 9 mg tablets	Budesonide 9 mg MUPS tablets (BUD-IV)
Acid stage: 2 h	0	0
Buffer stage: 1 h	4 (34)	8 (15)
2 h	22 (12)	15 (8)
3 h	43 (15)	37 (3)
4 h	65 (8)	73 (1)
6 h	94 (2)	101 (3)
8 h	96 (2)	101 (3)
10 h	96 (2)	101 (3)
F2		60.30

Table 8: Kinetic models of drug release and correlation coefficient

Kinetic model	Correlation Equation	UCERIS	BUD-IV
Zero-order model	$Q_t=k_{0t}$	0.991	0.975
First-order model	$\ln (Q_0-Q_t) = -k_1t+\ln Q_0$	0.931	0.884
Higuchi diffusion model	$Q_t=k_Ht^{1/2}$	0.908	0.880
Ritger–Peppas model	$\ln Q_t=n\ln t+k_R$	0.982	0.981
Hixson–Crowell model	$(1-Qt)^{1/3}=1-k_{HC}$	0.965	0.936

Table 9: Pharmacokinetic parameters of budesonide reference product and optimized formulation (BUD-IV)

Pharmacokinetic parameters	Reference	Optimized formulation
C max (ng/ml)	1.64	1.75
AUC 0-t (ng. h/ml)	19.50	19.29
AUC 0-inf (ng. h/ml)	20.43	20.27
T max (h)	18.50	15.33
t 1/2 (h)	5.90	4.63
K el (h-1)	0.15	0.15
%CV of C max	32.42	13.87
%CV of AUC 0-t	38.75	21.03
%CV of AUC 0-inf	39.09	19.91

Table 10: Budesonide 9 mg MUPS tablets stability studies

Test parameters	Initial		40°C/75% RH HDPE		
			1 month	2nd month	3 month
Dissolution (by HPLC)	% Drug release at acid stage				
	2 hr	0	0	0	0
	% Drug release at buffer stage				
	1 hr	8	3	4	3
	2 hr	15	13	21	19
	3 hr	37	27	44	44
	4 hr	73	69	77	79
	6 hr	101	96	98	96
	8 hr	101	96	99	96
	10 hr	101	97	99	96
Assay (%)	99.9		101.7	100.1	101.6
16 α-hydroxyprednisolone	0.007		0.006	0.001	0.002
D-homobudesonide	0.016		0.024	0.007	0.000
21-dehydrobudesonide epimers	0.018		0.056	0.149	0.202
11-keto budesonide	0.127		0.169	0.206	0.227
Highest unknown	0.048		0.125	0.307	0.223
Total related substances	0.216		0.380	0.733	0.925

and *in vitro* dissolution profiles and in vivo pharmacokinetic parameters (Cmax, AUC 0-t, AUC 0-inf) are similar that there is no significant difference compared to innovator. The drug release, drug content, and relative substances remain significantly no change after storage of 3 months 40°C/75% RH, suggested that budesonide is stable in MUPS formulation. Finally, it could be concluded that MUPS technology is one of excellent approaches to prepare targeted, controlled release dosage forms with less unit-to-unit variability in both *in vitro* and *in vivo* conditions.

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