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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BUDESONIDE PELLETS CONTAINING NATURAL GUMS FOR COLON TARGETING

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ABSTRACT
Pellets formulation with natural gums. The formulation of an enzyme as well as pH dependant pellets containing natural gums such as Mornings oleifera gum Lam. (MOG) and Cyamopsis tetragonolobus gum Taub. (CTG) were used for enzyme dependant release and further coating is provided to shows colon-specific delivery. Extrusion and spheronization techniques were used for the preparation of pellets. Pellets of budesonide evaluated for various properties such as flow behavior, physical properties such as sphericity, roundness, aspect ratio, hardness, and friability also investigated in vitro and in vivo targeting in rabbit. Preparation of pellets was done by using extrusion and spheronization method with the use of optimized concentration of gums those were 7.5% and 10% for CTG and MOG respectively and proportion of solvent mixture of water and Isopropyl alcohol in the ratio of 80:20. Pellets of budesonide evaluated for various properties includes flow behavior, physical properties such as sphericity, roundness, aspect ratio, hardness, and friability and found that all properties as per official limit also in vitro release study found that release of uncoated pellets in a sustained manner in 0.1N HCl for 2h due to swelling of natural gum, therefore further step of the coating was done in fluidized bed coater to prevent the release of drug in the upper part of GIT and after coating found that In vitro release of drug at the colonic environment and it confirmed with in vivo investigation in rabbit with X-ray examination of targeting and found that pellets reach at colonic part without disintegration. The use of natural gums for preparation of pellets in optimized concentration and wetting agent produce a formulation with all required chemical and physical properties and it gives effective in vitro release and also shows In vivo targeting in rabbit and due to use of natural gum for preparation of pellets also reduce some problems of metabolism of synthetic excipients.

KEYWORDS: Budesonide, pellets, *Mornings oleifera* gum, *Cyamopsis tetragonolobus* gum, *In vivo* colon targeting.

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INTRODUCTION
Ulcerative colitis (UC) is the disease affected at the distal part of the colon and in the case of conventional formulation, some difficulties for targeting the drug at the colonic site due to absorption of the drug from the upper part of GIT and very less amount of drug reaches at the colonic site to show pharmacological effect. Budesonide is a drug used in the treatment of ulcerative colitis but the problem associated with Budesonide is that it gets degraded in the stomach due to acidic pH and various enzymes are responsible for decomposition and also very less amount present at the colonic site when administered oral[(1)], therefore now a day various intrarectal formulation of Budesonide used in treatment for UC, it shows selective binding to corticosteroid receptors and acts as an anti-inflammatory[(2)] but there are some problems for intrarectal enema due to lack of patient compliance with the use of intrarectal formulation and enemah shows the local effect for a very small area[(3)], Some enteric-coated tablets are also available to overcome the problem related with intrarectal but in general case single formulation containing drug may be chances of accidental release of drug at the upper part of GIT and very less amount of drug can reach the affected site. So to avoid these types of the problem some multi particular system were prepared in form of microencapsulation [(4)], enteric coated pellets[(5)] to fulfill limitation of a monolithic system.

In the present work, we focus on the preparation of colon targeted pellets containing Budesonide with two natural gums *Mornings oleifera* gum(MOG) and *Cyamopsis tetragonolobus* gum(CTG), these gums contain polysaccharide act as prebiotics which also responsible for the growth of commensals which are responsible for the prevention of colitis as per various research carried out on this particular topic[(6)], So aim of present work is that preparation of pellets containing an agent which also shows adjuvant effect in the therapy of colitis.

The extrusion-spheronization technique used for the preparation of pellets in an easy, cost-effective, and reproducible formulation which can be scale up for industrial production[(7,8)], these gums are act as release retardant as well as a binder for pelletization process, In different proportion of gum by preliminary studies to follows specific properties includes particle size, sphericity, roundness, aspect ratio, hardness and release to select optimum proportion of gum for

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further processing also interaction of excipients with the drug were determined by using FTIR and DSC studies to confirm the compatibility of the formulation. After release studies of formulation, it confirmed that only single release retardant cannot fulfill the requirement of targeting to the colonic site therefore further development of formulation is done with an enteric coating of pellets by using Eudragit S100 in Fluidized-bed coater with optimizing various parameter and analyzed with SEM analysis for confirmation of coating and *in vitro* release study of coated pellets to find the release of drug prevent at pH of the upper part of GIT and show better release at colonic pH of the drug and confirmation of release with in vivo X-ray examination.

MATERIAL AND METHODS

MATERIALS

Budesonide provided as a gift sample from Cipla, Ltd. Mumbai, India, *Moringa oleifera* gum was collected from the plant by incision method, *Cyamopsis tetragonolobus* gum (Guar gum) and Microcrystalline cellulose (Avicel-PH 101) were purchased from Research-lab Fine chemical industries, Mumbai, Isopropyl alcohol (IPA) from Loba Chemie, Mumbai, Deionized distilled water was used.

PREPARATION OF PELLETS

Budesonide and excipients were accurately weighed mixed with uniform triturating and wetting agent water and IPA in the ratio of 80:20 added amount to form a damp mass. The damp mass was passed through extruder of single screw with axial die (S.B. Panchal, UTSE60) through a metal sieve of 1 mm apertures to obtain uniform extrude at operational speed 80 rpm. Obtained extrudes were added in a spheronizer (S.B. Panchal, USPH75) at 1000 rpm and for a duration of 10 minutes using a 2 mm friction plate with cross-hatch grooves pattern to obtained uniform shape pellets. The pellets drying was done at room temperature for 24 h[8,9].

Table 1: Formulation Table for Budesonide pellets

Ingredient	Bud MOG	Bud CTG
Budesonide	0.9g	0.9g
Microcrystalline cellulose	8g	8.5g
Moringa Oleifera Gum	1g	-
Guar gum	-	0.5g
Water:IPA	80:20	80:20

Coating of pellets

Coating with enteric polymer Eudragit S100 was done in wuster type R&D scale coater (ACG Pharma Technology Pvt. Ltd.). Coating dispersion of polymer was prepared by dispersing 10% w/v Eudragit S100 in the solvent proportion of 90:10 (IPA: water). Plasticizer used to impart flexibility film with 5% w/w Dibutyl phthalate with respect to polymer, dispersed with polymer in the solvent mixture and finally Talc and Titanium dioxide as anti-adherent and opacifier in 0.5% w/w in dispersion. (Hamedelniel and Pintye-Hodi 2011; Kaffash et al. 2019).

Compatibility Study

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry of pure Budesonide, MOG, GG, and pellets was analyzed to study chemical interaction for compatibility after the formation of pellets. DSC thermogram was obtained using DSC (SHIMADZU Crio-DSC, Japan) 10 mg of each ingredient and formulation was placed in aluminum pans and hermetically sealed and the study was carried out at a heating rate of 20°C/min from temperature 0°C- 300°C as per standard protocol and compared graph with previous studies[10,11].

Infra-Red (IR) Spectroscopy

The powder sample of the Budesonide was kept for drying for about 24hr to removed moisture content to avoid error in result due to moisture content. The powder sample of the budesonide and other excipients were mixed separately with KBr at 1:100 ratios in mortar and pestle and kept in a sample holder for analysis. For estimating compatibility of other excipients MOG, GG, and Avicel PH101 with Budesonide mixed with KBr and determined FTIR spectra recorded using FTIR spectrophotometer (SHIMADZU DR-8031, Japan). The wavelength ranged from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}[8,12-14].

EVALUATION

Determination of %Yield

Tapped density apparatus used to measure bulk and tapped density of the pellets. % yield of pellets was calculated by using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100 \quad (1)$$

Determination of Physical properties

Hardness

The Digital pellet hardness tester was used to check the hardness of pellets (Veego 01/0110)[8].

Determination of flow properties

Flow properties Angle of repose for determination of flow from the hopper to cavity used by using a funnel and calculated with equation 1, bulk and tapped density were determined by using ta bulk and tapped density apparatus and by using those values Carr's index and Hausner's ratio were determined by equation 2 and 3.

$$\text{Angle of repose } \tan\theta = \frac{h}{r} \quad (2)$$

Where h= Height of pile and r= radius of the circle

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \quad (3)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (4)$$

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Sphericity, Aspect ratio, and Roundness

Pellets images were analyzed with a Scanning electron Microscopy (SEM) and various diameter analyzed by ImageJ software to find the Surface area (A), longest length (dmax), and shortest length (dmin), and perimeter (P) were measured, and shape factors sphericity, roundness, and aspect ratio were calculated by following formulas 5, 6, and 7.

$$\text{Sphericity} = \frac{4\pi A}{P^2} \quad (5)$$

$$\text{Roundness} = \frac{P^2}{4\pi A} \quad (6)$$

$$\text{Aspect ratio} = \frac{dmax}{dmin} \quad (7)$$

Where A is an area, P perimeter, dmax longest, and dmin shortest diameter of pellets. The standard range for sphericity from 0 to 1, poor spherical value is 0 and perfect sphere shows value is equal to 1 and for roundness value close to 1 indicates more smooth and a value greater than 1.20 observed not that much smooth[12,15-17].

Scanning Electron Microscopy (SEM)

The surface morphological study was performed on coated and uncoated pellets using a scanning electron microscope (Supra 55, Carl Zeiss, German). The sample was fixed on SEM stub using double-sided adhesive tape, then the sample was coated with a thin layer of gold under vacuum and sample stub kept in SEM chamber, operate at 10kV and run samples at different magnification to analyze shape and surface characteristics[3,18,19].

Drug Content

Budesonide pellets were weighed accurately equivalent to 100 mg of drug and crushed in a mortar and dissolve in 100 ml solution methanol and sonicated for 30 minutes. Made dilution twice with 1ml in 10 ml volumetric flask and sufficient volume made up with further diluted with 6.8 pH phosphate buffers. The solutions evaluates at 246 nm using a UV/Visible spectrophotometer. Absorbance obtained from the analysis was used for the calculation of drug content[20].

Drug content was determined by using the following formula:

$$\% \text{ Drug content} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \quad (8)$$

Drug Release of uncoated pellets

In vitro release study for Budesonide uncoated pellets containing MOG and CTG were carried out in dissolution apparatus by placing the weight of pellets equivalent to 100mg of Budesonide into Type-I apparatus of dissolution tester (Electrolab dissolution tester). The dissolution media of 900 mL of 0.1N HCl was kept at 37.0 ± 0.5°C. The rotational speed of the baskets was set at 75 rpm. A sampling of media was done at 15 min intervals of 5ml sample and replaced with 5ml fresh medium up to 2 hours analyzed on U.V. Spectrophotometer at 246 nm wavelength (Shimadzu 1800). Release kinetics of formulation were determined by plotting release data with various release pattern which includes zero-order, first-order, Higuchi, Hixon Crowell and Korsmeyer peppa's [7, 18, 21].

Drug Release of coated pellets

In vitro release of enteric-coated pellets of Budesonide was carried out in USP dissolution tester by placing pellets in USP Type-I apparatus basket weight of pellets equivalent to 100 mg Budesonide (Electrolab dissolution tester). The dissolution media of 900 mL of 0.1N HCl was kept at 37.0 ± 0.5°C. The rotational speed of the baskets was set at 100 rpm. A sampling of media was done at 15 min interval of 5ml sample and replaced with 5ml fresh medium up to 2 hours analyzed on U.V. Spectrophotometer at 246nm wavelength (Shimadzu 1800) The followed by replacing dissolution media and performed release study for 2h in pH 6.8 phosphate buffer and 4 h at pH 7.4 buffer sample analyzed on U.V. Spectrophotometer at 246 nm wavelength (Shimadzu 1800) [22-24].

***In vivo* roentgenographical study**

The *in vivo* targeting study was performed by using New Zealand white rabbits due to anatomical and physiological similarity with the human subject. In vivo study was performed as per protocol approved by the IAEC of SBSPMs, B. Pharmacy College, Ambajogai as per guidelines of Control and Supervision of Experiments on Animals, CPCSEA Committee (SBSPM/BPHARM/IAEC/2020-21/01). Animals were kept for overnight fasting and pellets of an optimized batch of CTG and MOG containing radio-opaque substance 40% BaSO4 was used in the pelletization process. After overnight fasting, the optimized enteric-coated pellets filled in the capsule of size 1 and administered by peroral route with the use of capsule injector followed by flushing with 40 to 50 ml water. The X-Ray images were captured using a horizontal X-Ray machine (Siemens). The rabbit was placed in an upstanding position for the imaging process. The X-ray images were taken at the time interval of 1, 2, 4, 6, 7 and 8 h. [25, 26]

RESULTS

Compatibility study

FT-IR

Determination of interaction was done with FTIR studies of Budesonide and excipient. In the IR spectrum of Budesonide, functional groups observed that C-N-C cyclic (1216.61, 1266.28, 1309.19, 1334.27, 1374.77 cm^{-1}), C=O carbonyl group of cyclic ether (1662.69 cm^{-1}) it conjugation shows decrease stretching tendency, C-O Alcohol and ether (1101.39, 1298.14 cm^{-1}), C-H alkene out-of-plane bending (952.87 cm^{-1}), and $–CH_3$ bending (1411.94 cm^{-1}) which are the

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functional groups of Budesonide. The observed frequencies such as in 1662.69 and 3512.49 cm^{-1} were attributed carboxylic group and alcoholic group, respectively FT-IR spectra given in supplementary file S1-4.

DSC

The pure Budesonide showed two endothermic peaks at 226 and 259.31°C that corresponded to the drug melting point due to the crystalline nature of the drug. Moringa Oleifera Gum shows broad peak 223.41°C onsets 209.32°C and End set 244.92°C.

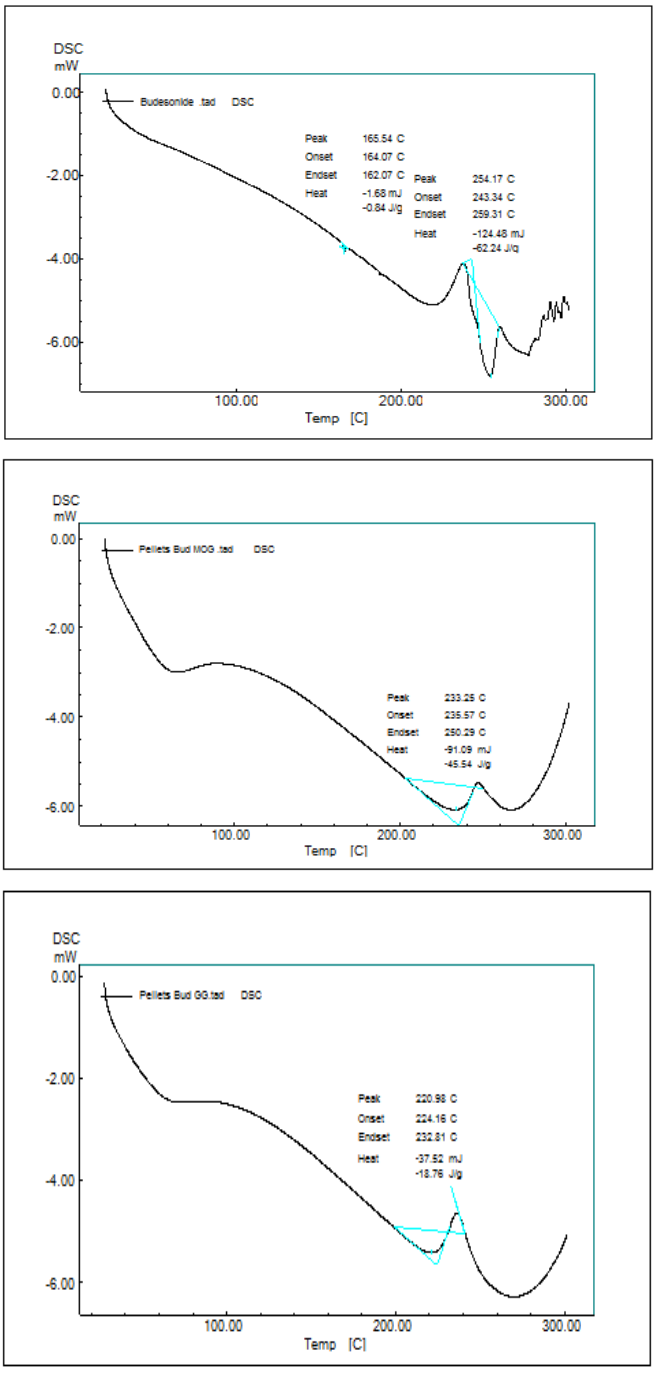

Figure 1: DSC curve for Budesonide, CTG pellets, and MOG pellets

Flow properties of pellets

Table 2: Flow properties of Budesonide pellets

Sample	Angle of repose (°) ± SD	Flow rate (g/sec) ± SD	Carr's index ± SD	Hausner's ratio ± SD
Bud CTG	29.98±1.64	1.12±0.08	10.75±0.73	1.1204±0.05
Bud MOG	28.53±1.52	1.02±0.05	15.55±0.50	1.1808±0.01

Flow properties of pellets were determined to flow behavior for uniform flow and also maintain weight uniformity of formulation by using Angle of repose, Carr's index, and Hausner's ratio shown in table 4. All parameters were found within the limit angle of repose value 29.98°±1.64 and 28.53°±1.52 for Bud CTG and Bud MOG respectively indicates the good flow behavior of pellets. The Carr's index for both gums containing pellets show up to 15 and Hausner's ratio was found to be near 1 it indicates the good flow behavior of pellets formulation of both gums.

Physical properties pellets

Table 3: Physical properties of Budesonide pellets

Sample	Yield (%)±SD	Hardness (kg) ±SD	Friability (%)±SD	Drug content uniformity (%)±SD	Sphericity ±SD	Roundness ±SD	Aspect ratio ±SD
Bud CTG	75.21±3.78	0.381±0.17	0.58±0.13	97.65±2.05	0.905±0.055	1.19±0.012	1.04±0.03
Bud MOG	82.16±2.59	0.297±0.18	0.65±0.10	95.40±1.16	0.912±0.047	1.20±0.08	1.02±0.02

Physical properties were evaluated which include %Yield, Hardness, Friability, sphericity, roundness, and aspect ratio are shown in the table. Percentage Yield for MOG was found in a higher range as compared to CTG with the reproducible result. Hardness for CTG is more as compared to MOG may be due to nature of gum, CTG produces more sticky mass as compared to MOG, therefore, it affects on both Yield and Hardness also it affects on the friability of formulation of CTG is less as compared to MOG and limit of friability for both gums as per official standard. The sphericity of both gums was found near to 1 indicates that pellets for gum are nearly spherical. Roundness near to 1.20 indicates the smooth surface of pellets both gums pellets shows the nearly standard value.

In vitro drug release studies for uncoated pellets

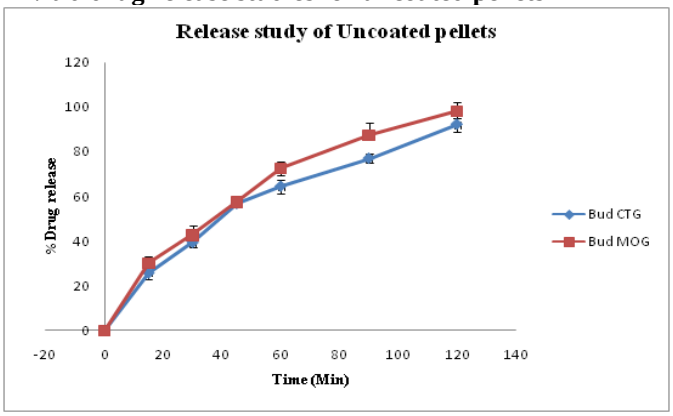

Figure 2: Figure showing release study of Budesonide MOG and CTG uncoated pellets

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The release study of uncoated Budesonide pellets was performed in 0.1N HCl. It shows the release of the drug in the control pattern for 2h with the concentration of release for 98.21±3.14 and 92.13±2.98 for pellets of MOG and CTG respectively. The release pattern of drug with the different kinetic model with respective regression coefficient for various model shown in table 6[27]. The release exponent was determined as per Peppas model found that values between 0.48 and 0.98 for spherical shape particles0.45 to 0.89 it means that the release pattern of the drug is diffusion and swelling of matrix pellets due to the presence of hydrophilic gums[28,29].

Table 4: R^2 values for different release pattern for pellets of MOG and CTG

Batch No.	Bud MOG	Bud CTG
Model name	R^2	R^2
Zero order	0.923	0.925
First order	0.937	0.969
Huguchi model	0.989	0.99
Hixson	0.887	0.887
Korsmeyer peppas	0.99	0.988

1. *In vitro* release study of coated pellets

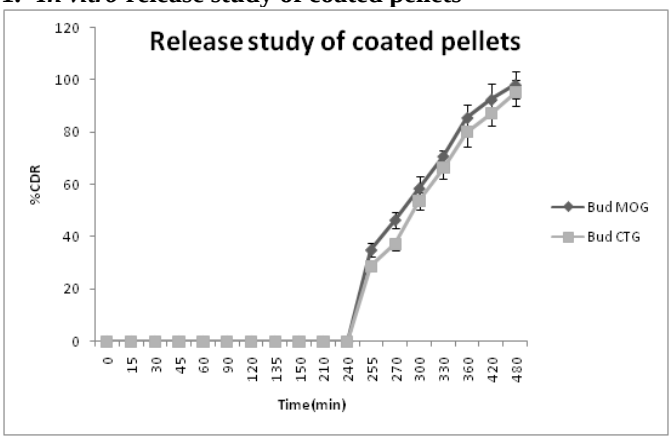


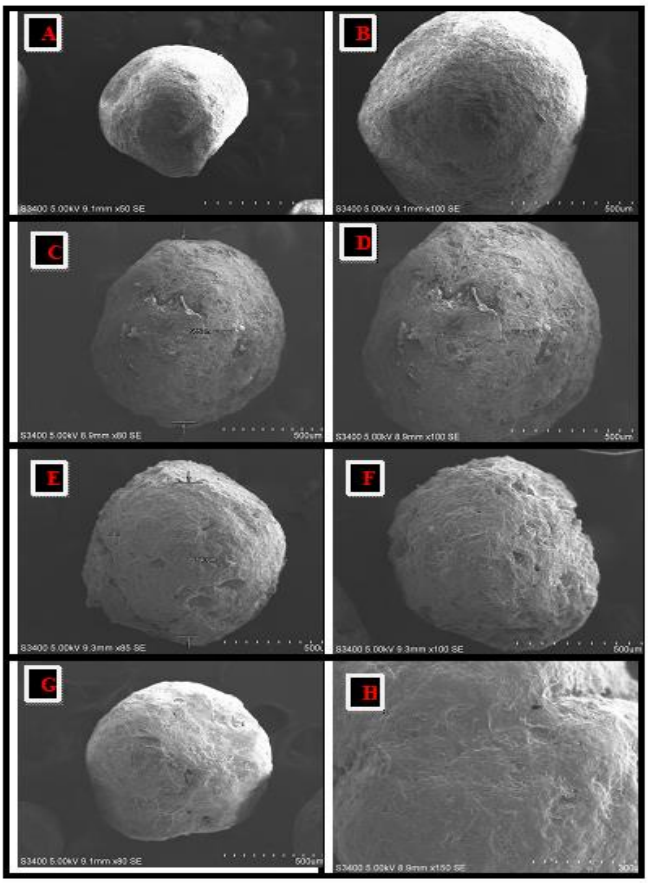
Figure 3: Release curve of Budesonide MOG and GG coated pellets

In vitro release study of coated pellets showed no release at 0.1N HCl and 6.8 pH phosphate buffer up to 4h and media changed with 7.4 pH phosphate buffer showed release in sustained pattern for 4h more than 85% drug release into 2.5h and remaining drug release at the end of the dissolution process.

SEM analysis

SEM images of uncoated and coated pellets shown in figure pellets of MOG shows nearly spherical and less porous as compared to pellets of CTG. The pores of pellets are covered after coating and coated pellets show uniform surface coating of pellets.

Figure 4: SEM images of uncoated and coated pellets at different magnification A. Uncoated MOG pelletsX80 B. Uncoated MOG pelletsX100 C. Coated MOG pelletsX80 D. Coated MOG pelletsX100, E. Uncoated CTG pellets X80 F. Uncoated CTG pellets X100, G. Coated CTG pelletsX80 and H. Coated CTG pelletsX150



In vivo roentgen graphical study

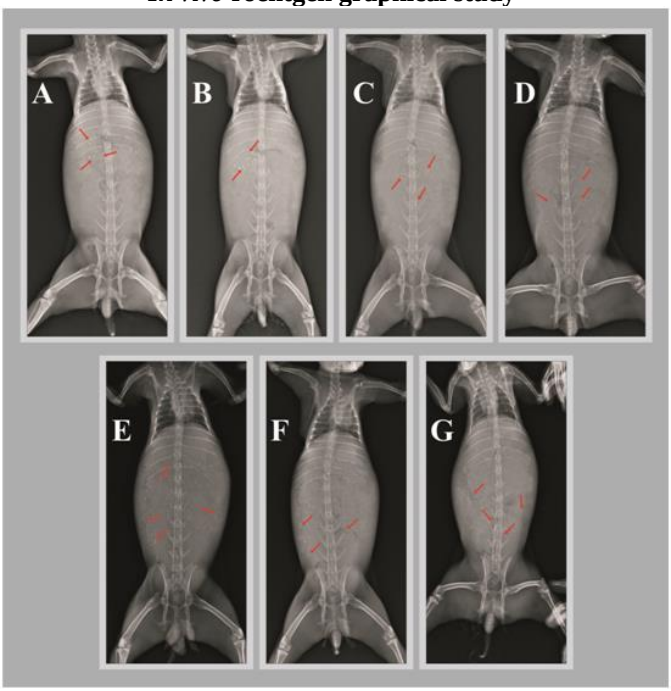


Figure 5: Roentgenogarphical study in rabbit (A-G) behavior of enteric-coated pellets

The *In vivo* roentgenographic study shown in the image of X-ray examination of Budesonide shown after two images show

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pellets remain in the stomach after 2h pellets start the movement from stomach to small intestine and finally it enters into colonic part and size of pellets started decreasing indicates that disintegration of pellets start at the colonic site.

DISCUSSION

In the present study of the formulation of Budesonide pellets for colon-specific delivery use of natural gum, the formulation was prepared by using an optimized concentration of gum and wetting solvent. The compatibility study was performed to find the interaction of budesonide and excipient with IR and DSC studies, In IR spectra found that all characteristic peaks of the Budesonide in FT-IR spectra of the physical mixture and pellets indicate indicates that functional group peaks are observed with little changes in peaks it indicates that a lack of chemical interaction in the drug and other excipients. Reference FT-IR spectrum of the drug was compared used in other studies to find the compatibility of drug and excipient and it has been found that their lack of interaction [(12)]. The DCS data for Budesonide pellets containing Moringa Oleifera gum observed a broad endothermic peak with two peaks of Budesonide with approximately the same temperature in pure form which indicates that very little interaction of Budesonide and other excipients. The DSC thermogram was compared with other graphs to check the purity of the product[(2) (5)].

The Budesonide pellets were prepared with natural gums as a binder as well as control release for drug at colonic site selection of formulation parameters were done as per earlier factorial study for another drug which includes that effects of different parameter on properties of pellets those parameters were concentration of gum and solvent for preparation of damp mass, according to that study found that at lower concentration of gum shows difficult to form damp mass and in a higher concentration of gum shows that non-spherical pellets formation and due to use of deionized water alone in preparation pellets shows that sticking of material to extruder and spheronization process found in the preliminary study therefore nonpolar solvent Isopropyl alcohol used in different ratios to prevents different processing problems. After optimization studies, it found that 7.5% concentration of CTG and 10% concentration of MOG with 80:20 proportion of water and Isopropyl alcohol shown that proper release, Hardness, %yield, sphericity, roundness, and aspect ratio.

The release studies of uncoated pellets of Budesonide showed that control release of drug for two hours in 0.1N HCl might be effect by swelling of hydrophilic gum matrix, for further detail understanding various release models were studied to find release pattern of drug from gum matrix it showed that specific values for Korsmeyer Peppas model indicate that swelling and diffusion release with the non-fickian pattern of release found from release exponent data[(30)].

The release study indicates that drug shows release with swelling at the upper part of GIT for improvement of drug release performance at specific site further step of coating with enteric polymer to show specific release and also single release retardant is difficult to target specific site so the conversion of matrix system to the reservoir with coating and it showed expected to release at colonic media in *In vitro* analysis. *In vivo*, X-ray examinations were performed to confirm the release of drug at the colonic site shown that movement of formulation from the stomach to colon with specific time interval at 8h it shown pellets reach the colonic site. SEM analysis showed that pellets of MOG and CTG showed some porous in nature it may be evaporation of wetting solvent Isopropyl alcohol after at drying stage and pores covered with coating.

CONCLUSION

It has been concluded from the present study is that use of natural gums for preparation of pellets in optimized concentration and wetting agent produce a formulation with all required chemical and physical properties and it gives effective *in vitro* release and also shows *In vivo* targeting in rabbit and due to use of natural gum for preparation of pellets also reduce some problems of metabolism of synthetic excipients.

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