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DESIGN AND DEVELOPMENT OF ORAL COLON TARGETED DRUG DELIVERY SYSTEM OF DEXAMETHASONE

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ABSTRACT

Inflammatory bowel disease (IBD) afflicts approximately four million people across the world, usually before the age of 40. It describes two major chronic, non-specific inflammatory disorders of the gastro-intestinal (GI) tract, ulcerative colitis (UC) and Crohn's disease (CD), the causes of which remain unknown. UC is usually limited to the colon and rectum. The colon and rectum are parts of the body's digestive system which remove nutrients from food and stores waste until it passes out of the body.

The present study was aimed at developing dexamethasone matrix tablets by direct compression technique. The compatibility of drug, polymer and excipients were determined by I.R. spectroscopy analysis. For precompression evaluation, the powder mix was subjected to micrometric evaluation (bulk density and Carr's Index) and drug content uniformity to check the mixing uniformity, after which matrix tablets containing various proportion of guar gum ranging from 40 to 80% of guar gum and immediate release (reference formulation) containing 5% sodium starch glycollate (superdisintegrant at 5% level) were prepared, and subjected to thickness, diameter, weight variation, hardness, friability and drug content uniformity. After these studies the matrix tablets containing 40 to 60% were subjected to in-vitro release studies in 0.1N HCl (2h), pH 7.4 Sorensen's phosphate buffer (3h) and simulated colonic fluids (rat caecal content medium at 4% w/v level after 7 days of enzyme induction), than potential formulations (containing guar gum 50% and 60% as carrier) were subjected to scanning electron microscopy (SEM) to examine the surface topography, texture of the formulations, morphology of fractured or sectioned surfaces and to analyze the surface

of polymeric drug delivery systems that provided important information about the porosity of the device and swelling changes in the matrix of the formulations by subjecting the formulations to SEM in dry state. At the end short term stability studies were carried out at 37^0C/60% RH and 50^0C/75% RH for a specific time period up to 30 days for selected formulation (containing guar gum 50% and 60% as carrier) and were analyzed for the physical evaluation like appearance (color) and hardness and chemical evaluation like determination of drug content and drug polymer compatibility.

Keywords: Inflammatory bowel disease, Matrix tablets, Direct compression, Colonic release, Scanning electron microscopy.

INTRODUCTION

Corticosteroids were the first agents demonstrated in controlled trials to have efficacy in UC. Although the mode of action remains undefined, there is a growing body of evidence in the literature that implicates leucocytes-endothelial cell adhesion as a principal target for these compounds. The most promising of the colonic drug delivery systems especially for IBD involving formulations that are dependent on the enzymatic action of colonic bacteria are those based on polysaccharides. Polysaccharides are biodegradable, abundantly available and also cheap. The polysaccharides that are under active investigation for colon-specific drug delivery include pectin and its salts, chondroitin sulphate, amylose, dextran, guar gum and chitosan. Earlier, it was reported that guar gum is a potential carrier for colon-specific drug delivery. Guar gum is a polysaccharide derived from the seeds of cyamopsis tetragonolobus, family Leguminosae. It consists of linear chains of (1→4)-β-D-man nopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. It is cheap, safe and abundantly available and is being used in pharmaceutical formulations as disintegrant, suspending agent, thickening agent and binder. In the light of above information guar gum-based colon targeted drug delivery systems may be useful for the prevention and treatment of inflammatory bowel disease (IBD).

The degradation of guar gum in the simulated colonic fluids by the action of bacterial enzymes is well documented. For example, Wong et al (1997) demonstrated that the galactomannanase (>0.1%) accelerated dissolution of dexamethasone and budesonide from guar gum matrix tablet containing 60.5% of guar gum, and the extent of drug dissolution depended on concentration of galactomannanase. In another two studies also the inclusion of

galactomannanase, α-galactosidase or β-mannase (enzymes which act on guar gum) in the dissolution medium degraded guar gum or its derivatives and thereby released the drug contained in the guar-based formulations. In this context, it was reported that guar gum is a potential carrier for colon-specific drug delivery. The objectives of study includes formulation and evaluation of guar gum-based and immediate release tablets of dexamethasone and subject them to in-vitro drug release studies so as optimize the colon-targeted tablet formulations for their ability to deliver the drug to the physiological environment of colon without being significantly released in stomach and small intestine. The guar gum matrix tablet formulation providing an optimal in vitro drug release was subjected to further studies to investigate its in vivo performance in healthy volunteers.

MATERIALS

Dexamethasone I.P. was gratis sample from Arbro Pharmaceuticals Ltd., New Delhi, India, Microcrystalline cellulose (Avicel, FMC Type PH-105) was gift sample from Signet Chemical Corporation, Mumbai, India, Sodium starch glycolate was gift sample from CFL Pharmaceuticals Ltd., Goa, India. Guar gum (USP/NF)] was purchased from Loba Chemie Pvt. Ltd., Mumbai, India, Absolute ethanol 99.9% (water maximum 0.02%), sodium chloride extrapure, Magnesium Stearate and talc were of pharmacopoeia quality (USP/NF) and hydrochloric acid 35-38% LR was purchased from S.D.Fine Chem Limited, Mumbai-400025, India. Potassium dihydrogen orthophosphate (assay 99.0-101.0%), Dibasic sodium phosphate (di-sodium hydrogen orthophosphate anhydrous) and Sodium Phosphate Monobasic (Sodium Biphosphate) was purchased from Ranbaxy Fine Chemicals Limited, New Delhi, India, anaesthetic ether – I.P. was purchased from tkm Pharma, Hyderabad-500020, India, nitrogen gas and regulator was purchased from Supreme Traders, Dharwad Road, Belgaum-590016, India, male albino rats weighing 150-200 g purchased from Shri. Venkateshwara Enterprises, Bangalore, India.

METHODS

Preparation of Dexamethasone matrix tablet

Matrix tablets of dexamethasone were prepared by direct compression method. Microcrystalline cellulose (Avicel PH-105) was used as diluent, in reference formulation (immediate release dexamethasone tablets) a superdisintegrant such as sodium starch glycollate was incorporated at 5% level for rapid disintegration of tablet and a mixture of talc and magnesium stearate (2:1) was used as lubricant. Guar gum was included in the colon-

targeted formulations in various proportions. The composition of different colon-targeted formulations and immediate release formulation used in the study containing 9 mg of dexamethasone in each formulation is shown in Table 1. In all the colon-targeted formulations, guar gum and M.C.C. was sieved (250 μm) separately and dexamethasone was premixed with small amount of guar gum or M.C.C. and sodium starch glycollate (dry) 5% (in case of immediate release tablet) and magnesium stearate, talc by Spatulation method in glass mortar and pestle followed by mixing of remaining guar gum or M.C.C. (in case of immediate release tablet) by addition method. Powder mixture were transferred to the amber coloured bottle to protect the light sensitive dexamethasone from light for turbular mixing till half an hour. Micrometric properties [such as bulk density and Carr's index] were evaluated and uniformity of mixing was assessed by conducting powder content uniformity test on the powder mix samples before punching of tablets. [Samples collected from final powder blend (1 to 3 times unit dose) using a thief from 10 different locations (5 from top, 3 from middle and 2 from bottom) for blending uniformity test].

The powder mix was compressed manually into tablets with applied force of 7 ton (7000 kg) for guar gum tablets and 0.5 ton (500 kg) for immediate release tablets to keep the disintegration time <1min, using 10 mm round, flat and plain punches on a manual hydraulic press. (Hydraulic /Pellet Press, Type-WT, Manufactured by Kimaya Engineers, Thane, India) Tablets of each composition (as mentioned in table 1) were compressed (100 No.) shown in Plate 5.2 and evaluated for their hardness, determination of drug content, weight variation, friability test, thickness and diameter test, measurement of mass degree of swelling, measurement of gel strength and in-vitro drug release studies with a suitable number of tablets for each test.

***In Vitro* Drug Release Studies**

The ability of guar gum matrix tablets of dexamethasone to remain intact in the physiological environment of stomach and small intestine was assessed by conducting drug release studies under conditions mimicking mouth to colon transit. Drug release studies carried out using dissolution rate test apparatus USP XXIII (Electrolab – Tablet Dissolution Tester TDP-06P,100 rpm, 37^0C) for 2h in 0.1N HCl (900ml). Then the dissolution medium was replaced with pH 7.4 Sorensen's phosphate buffer (900 ml) and tested for drug release for 3 h. The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in rat caecal content medium. For this test apparatus

USPXXIII (Apparatus 1, 100 rpm, 37^0C) was slightly modified. A beaker (capacity 150 mL) containing 100 mL of rat caecal content medium was immersed in the water maintained in the 1000mL vessel, which, in turn, was in the water bath of the apparatus. The control study for this was also performed in 0.1N HCl (2h), pH 7.4 Sorensen's phosphate buffer (3h) and pH 6.8, PBS without rat Caecal contents. About 1 mL of absolute ethanol was added, to the dissolution sample (1 ml each) stored in 10 mL volumetric flask, the sample was sonicated well for complete dissolution of the drug and made up to the volume with methanol. The mixture was centrifuged, filtered through G-5 borosil (bacteria proof filter) and was analysed for dexamethasone by UV-spectrophotometric method. After completing in vitro release studies the cumulative percent of dexamethasone released from guar gum matrix tablets (n=3) at different time periods with and without rat caecal contents was compared. The statistical significance was tested by using student's t-test. A value of $p<0.05$ was considered statistically significant.

The Scanning Electron Microscopic (SEM) Analysis was conducted using a JOEL JSM-T330A Scanning Microscope for the optimized formulations in three states involving Dry tablet surface, Tablet after swelling for 3 hours and Tablet after swelling for 8 hours, so as to determine particle size distribution, surface topography, and texture and to examine the morphology of fractured or sectioned surfaces.

After selecting optimum formulation from above studies tablets were subjected to short term stability studies at 37^0C/60% RH and 50^0C/75% RH for a specific time period up to 30 days for selected formulations, the selected formulations were analysed for physical evaluation appearance and hardness and for chemical evaluation as for drug content and drug-polymer compatibility studies.

RESULTS

In precompression evaluation, the loose bulk density (LBD), tapped bulk density (TBD) and Carr's Index (percentage compressibility) were found 0.3030 to 0.4764 gm/ml, 0.4464 to 0.6896 gm/ml, and 30.96 to 34.48%. The powder mix was found to contain 98.94 to 100.17% of the labeled amount. The disintegration time was found to be less than 60 seconds, and the hardness of the tablets was found to be in range of 0.43 to 5.74 kg/cm^2 and 4.30±0.296 kg/cm^2 respectively. The prepared tablets were subjected to thickness test, diameter test, weight variation test, hardness test, friability test and drug content uniformity test, and tablets

were found to be in range of 3.19±0.020 to 3.62±0.049 (mm), 10.04±0.008 to 10.11±0.008 (mm), 346.91±1.218 to 353.00±0.892 (mg), 0.43±0.210 to 5.74±0.309 (kg/cm^2), 0.223 to 2.961% and drug content uniformity 99.22 to 100.34% of the labeled amount respectively. All the tablet formulations passed the above tests except formulation DX-80, which failed the friability test. Prepared tablets were subjected to measurement of mass degree of swelling and gel strength, which were found to be in the range of 2.68 to 3.70 and 5.21 to 15.50 (ml) respectively.

***In vitro* release studies**

The percent of dexamethasone released from the DX-40 matrix tablets at the end of 24 hrs was found to be 100.74±0.251%. Whereas in control study (without rat caecal contents in the dissolution medium) only 77.95±1.268% of dexamethasone was released. The DX-50 released 99.47±0.338% of dexamethasone in the presence of rat caecal contents whereas in control study the formulation released only 47.20±0.608% of dexamethasone. The matrix tablets containing 60% of guar gum (DX-60) released only 61.53±1.235% of dexamethasone in rat caecal content medium at the end of 24 h whereas in control study it was only 24.97±0.185%. The results are summarized in table 2 and comparative results with immediate release formulation were as per table 3.

In vivo studies

In-vivo behaviour of tablet was determined by " Roentgenography" in dog. The guar gum (50%) based matrix tablet containing barium sulphate was seen in different photograph in Figure 1-4.

Potential formulations (DX-50 and DX-60) were subjected to Scanning Electron Microscopy (SEM) in dry state, swelling after 3 hrs and 8 hrs in the distilled water at the magnification X500.

Physical evaluation under short term stability studies like appearance (colour) and hardness after 10, 20 and 30 days along with chemical evaluation (drug content) in the same conditions as above mentioned. During the chemical evaluation to confirm the drug polymer compatibility by the I.R. spectroscopy, the spectra of formulations (DX-50 & DX-60) at the end of study after 30 days were obtained and compared with original spectras.

Tables:

Table 1: Composition of Dexamethasone Matrix Tablets containing 40% (DX-40), 50% (DX-50), 60% (DX-60), 70% (DX-70) and 80% (DX-80) of Guar gum and 5% Sodium Starch Glycollate (DX-IR*)

Ingredients	Quantity (mg) per each matrix /I.R. tablet					
	DX-40	DX-50	DX-60	DX-70	DX-80	DX-IR
Dexamethasone	9	9	9	9	9	9
Guar gum	140	175	210	245	280	--
Sodium starch glycolate (dry)	--	--	--	--	--	17.5
Microcrystalline cellulose (M.C.C.)	190.5	155.5	120.5	85.5	50.5	313
Talc	7	7	7	7	7	7
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5
Total (mg)	350	350	350	350	350	350

*** Immediate release**

Table 2: Mean±SEM Percent of Dexamethasone Released from Matrix Tablets Containing 40%, 50% and 60% of Guar gum (DX-40) in 0.1N HCl (2h), pH 7.4 Sorensen's Phosphate Buffer (3h) and pH 6.8 PBS with and without Rat Caecal Contents (19 h)

TIME (h)	MEAN±SEM PERCENT OF DEXAMETHASONE RELEASED					
	DX-40		DX-50		DX-60	
	Without rat caecal contents	With rat caecal contents	Without rat caecal contents	With rat caecal contents	Without rat caecal contents	With rat caecal contents
2	6.50 ± 0.185	6.36 ± 0.120	5.30 ± 0.057	4.83 ± 0.145	1.10 ± 0.152	1.400 ± 0.057
5	12.86 ± 0.121	13.21 ± 0.172	12.50 ± 0.404	11.87 ± 0.266	4.90 ± 0.152	3.83 ± 0.145
8	27.97 ±	38.22 ±	17.13 ±	19.10 ±	9.55 ±	10.80 ±

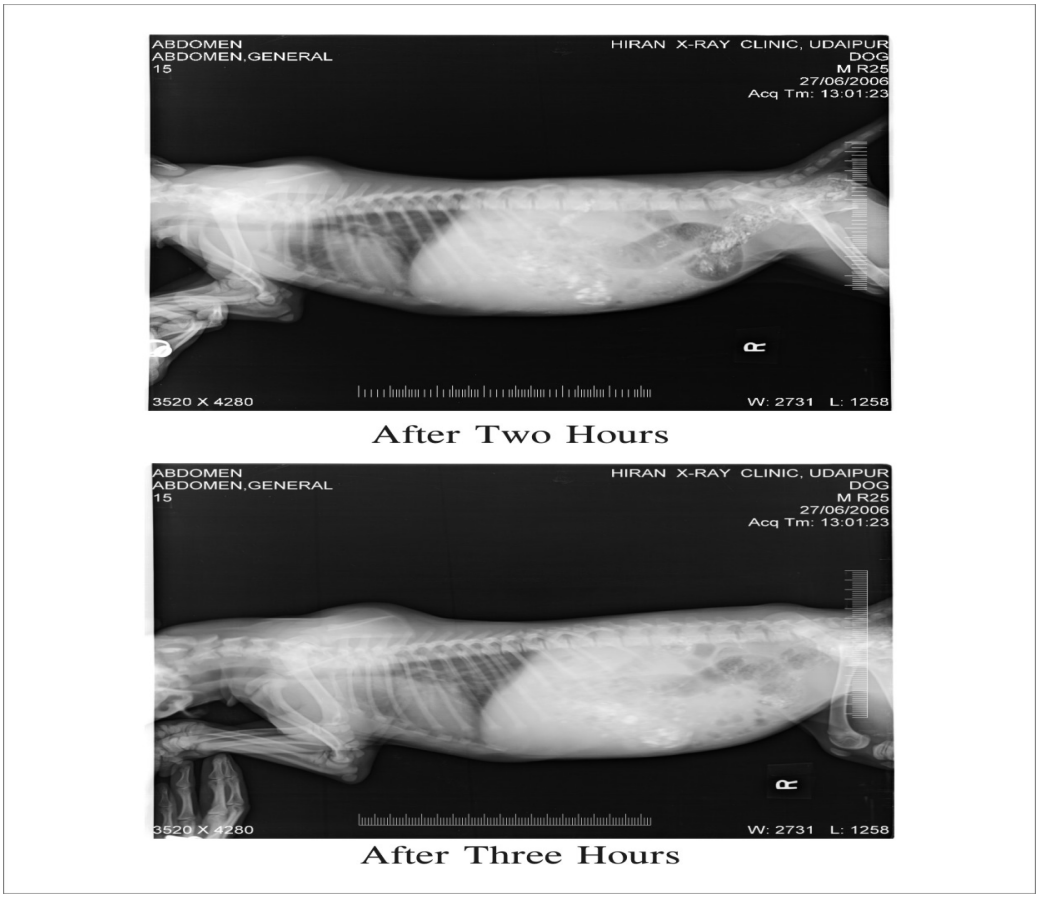
	0.380	0.180*	0.088	0.057*	0.076	0.057*
14	47.24 ± 0.540	75.33 ± 0.650*	28.00 ± 0.2517	48.5 ± 0.529*	15.67 ± 0.569	27.83 ± 0.405*
18	60.43 ± 0.630	91.35 ± 0.900*	36.00 ± 0.288	79.80 ± 0.929*	19.07 ± 0.753	39.40 ± 1.266*
24	77.95 ± 1.268	100.74 ± 0.251*	47.20 ± 0.608	99.47 ± 0.338*	24.97 ± 0.185	61.53 ± 1.235*

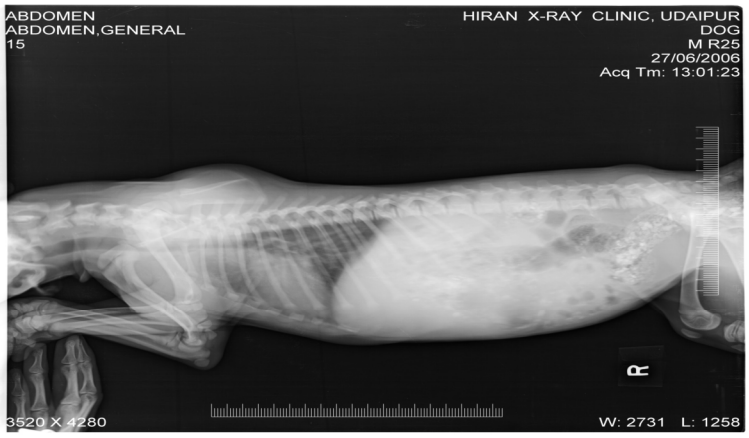
Table 3: Comparative account of in vitro release DX-IR*, DX-40, DX-50 and DX-60

TIME (h)	MEAN±SEM PERCENT OF DEXAMETHASONE RELEASED FROM			
	DX-IR*	DX-40	DX-50	DX-60
0.25	24.66 ± 0.088	0	0	0
0.50	52.3 ± 0.115	0	0	0
1.0	85.6 ± 0.0577	3.19 ±0.020	2.15 ± 0.050	0
1.5	91.56 ± 0.088	4.18 ± 0.018	3.55 ± 0.028	1.03 ± 0.040
2	95.5 ± 0.115	6.36 ± 0.120	4.83 ± 0.145	1.40 ± 0.057
5	----	13.21 ± 0.172	11.87 ± 0.266	3.83 ± 0.145
8	----	38.22 ± 0.180	19.10 ± 0.057	10.80 ± 0.057
14	----	75.33 ± 0.650	48.5 ± 0.529	27.83 ± 0.405
18	----	91.35 ± 0.900	79.80 ± 0.929	39.40 ± 1.266
24	----	100.74 ± 0.251	99.47 ± 0.338	61.53 ± 1.235

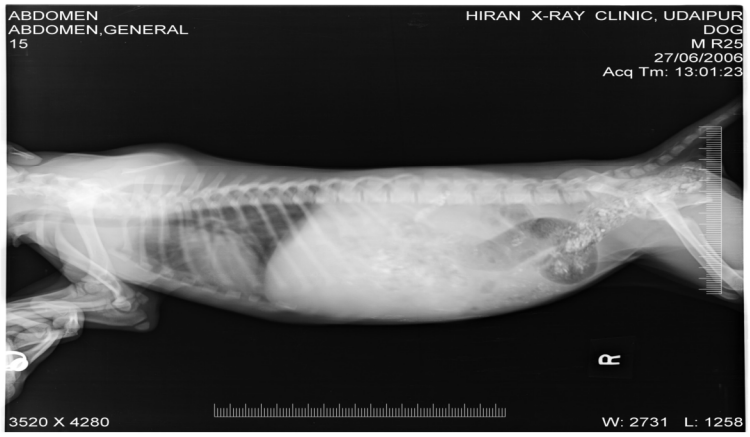
***(Immediate release)**

Figure 1-4: Roentgenographic studies in dog with guar gum (50%) based matrix tablet containing barium sulphate





After Seven Hours



After Eight Hours

DISCUSSION

The matrix formulations showed the high Carr's Index values, that indicating low compressibility of powder mix. The swelling of the guar gum-based formulations found linear with increasing percentage of guar gum. Uniformity of drug content proved mixing efficiency. The hardness and friability results of DX-70 and DX-80 may be due to higher guar gum content in the matrix tablets, and hence, the DX-70 and DX-80 formulations were not subjected to in-vitro drug release studies.

Dexamethasone tablets containing 40 to 60% of guar gum were subjected to 24 hours of dissolution study conducted with and without rat caecal contents in the dissolution medium (control). In the test matrix tablets containing 40% of guar gum (DX-40) degraded into 2-3 pieces at about 10 h of dissolution study in the presence of simulated colonic fluids (rat caecal content medium). A significant difference ($p<0.0001$) was observed in the amount of

dexamethasone released at the end of dissolution study (24 h) with rat caecal contents in the dissolution medium when compared to the dissolution study without rat caecal contents (Table 6.3 & Fig. 6.1). This may result in the release of the drug in the last part of the small intestine itself. The study shows that the release of dexamethasone in the physiological environment of colon is due to the microbial degradation of guar gum matrix tablets in the presence of rat caecal contents. The dissolution study was carried out without rat caecal contents (control study) to ensure that the drug release is not due to mechanical erosion that is likely to occur because of the bowel movements in humans. On exposure to the dissolution fluids, the guar gum gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core tablet. The hydration of guar gum seems not to be affected by the pH of the dissolution medium. A significant difference ($p<0.0001$) was observed at 24h in the amount of dexamethasone released from DX-50 when compared to dissolution study without rat caecal contents. Though the matrix formulation DX-60 released only 61.53±1.235% of dexamethasone in simulated colonic fluids, a significant difference was observed ($p<0.0001$) in the dissolution pattern at 24h of study when compared to the dissolution study without rat caecal contents (Table 6.9 and Fig. 6.3). Thus the matrix formulation DX-40 released almost the entire quantity of the drug within 18 h of the dissolution. The formulation DX-50 also released about 99.47% of its drug content at the end of 24 h of dissolution study whereas the formulation DX-60 released only 61.53%. The results of the in-vitro drug release study indicated that matrix tablets of dexamethasone containing 50% of guar gum is a potential formulation for targeting dexamethasone to the physiological environment of colon. Though the matrix formulation DX-60 released only 61.53±1.235% of dexamethasone in simulated colonic fluids, a significant difference was observed ($p<0.0001$) in the dissolution pattern at 24h of study when compared to the dissolution study without rat caecal contents (Table 6.9 and Fig. 6.3). Thus the matrix formulation DX-40 released almost the entire quantity of the drug within 18 h of the dissolution. The formulation DX-50 also released about 99.47% of its drug content at the end of 24 h of dissolution study whereas the formulation DX-60 released only 61.53%. The results of the in-vitro drug release study indicated that matrix tablets of dexamethasone containing 50% of guar gum is a potential formulation for targeting dexamethasone to the physiological environment of colon. After examination the photographic results obtained from SEM, it was observed from DX-50 (dry) and DX-60 (dry) that formulation DX-50 has smooth, plane and less sectioned (fractured) surface than the DX-60 in dry state. The less

sectioned (fractured) surface may be because of the less percent (50%) of guar gum in DX-50 than the DX-60 (60%). SEM of DX-50 after 3 hrs selling showed less swelled and more uniform gel with uniform matrix than DX-60, DX-60 after 3hr swelling showed more swelled and less uniform gel with uniform matrix may be due to the high percent of guar gum (60%) than 50% in the formulation DX-50. After swelling till 8 hr the formulation DX-50 & DX-60 both showed the formation of properly swelled gel with uniform matrix. Therefore it can be concluded that both formulation (DX-50 and DX-60) showed uniform matrix that proves the uniformity in mixing of all ingredients of formulations and swelled properly after 8 hrs swelling indicating good swelling property of guar gum.

In short term stability studies, during chemical evaluation it was concluded that formulations (DX-50 & DX-60) showed drug polymer compatibility. No change in color observed and minor increase in hardness may be due to the moisture loss at elevated temperature from guar gum (polymer). After storing at elevated temperature and humidity very minor decrease in the drug content may be because dexamethasone is prone to oxidative degradation in the presence of heat and moisture. At the end it was concluded in the light results obtained from stability studies that formulations (DX-50 & DX-60) are stable in above mentioned conditions. However the long term stability of the formulations needs to be studied. The roentgenography studies in dog suggested the pharmacokinetic pathway of the proposed formulation. The usefulness of this formulation (DX-50) in the humans is needs further in vivo and pharmacokinetic studies.

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