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Original Article

Formulation Development and *in-vitro* Evaluation of Sulfasalazine and Dexamethasone Combination Tablets Containing Natural and Semi Synthetic Polymer for Colon Targeting

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ABSTRACT

The present research was to develop oral sustained release tablets for colon targeting. Two drugs in combination form were used in this research to prepared tablets. Combination of sulfasalazine and dexamethasone used with natural and semi synthetic polymers (tragacanth and HPMC K15). Sustained release matrix tablets of sulfasalazine and dexamethasone were prepared by using different ratios of drug, HPMC K15 and tragacanth. Microcrystalline cellulose (MCC) and lactose were used as diluents. Both polymers were mixed with other ingredients and formed a matrix system using direct compression technique. All the ingredients of formulation were compressed using concave punches in ZP 19 compression machine. Compressed tablets were evaluated for assay, diameter, hardness, thickness, friability, weight variation and *in vitro* dissolution using USP dissolution apparatus type II. Different formulations were prepared and evaluated with respect to dissolution profile in 900 mL 0.1 N Hcl and phosphate buffer pH 6.8 and pH7.4 including microbial flora for 12 h at 37˚C. Rising the amount of polymer (HPMC K15) in the formulation led to slow release of drug and decreasing the amount of polymer gave enhanced release of sulfasalazine and dexamethasone. Different mathematical models used to evaluate the matrix system (Zero order, First order, Higuchi and Hixson-Crowell). T5, T7, T8 solid matrix formulations followed zero order and Higuchi. The results showed that the formulation T7 containing 17% HPMC K15 and 17% gum tragacanth gives better results in microbial flora with phosphate buffer.

Key words: HPMC K15, Tragacanth gum, Sulfasalazine, Dexamethasone, Sustained release.

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INTRODUCTION

Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration.[1] When highly water soluble drugs are produce for oral sustained release dosage form cause problems like they may be released more rapidly and produce toxicity if not prepared in appropriate procedure.[2] several methods are there to prepared colon targeted sustained release dosage form.[3] Among which matrix system is most appropriate due to efficiency, consistency, validation, scale up and cost effective. Microcrystalline cellulose and lactose were used as diluents.[4] Colon targeted drug delivery systems present a variety of benefits above conventional dosage forms that include decrease in dosage rate, minimum toxic effect and improved patient compliance.[5] On the other hand, more constant level of drug in the blood constant flow with minimum peak-valley is reached, achieve greater efficacy.[6] A process for manufacturing colon targeting extended release dosage form is expensive which makes these products expensive than the conventional dosage forms.[7,8] Other factors that we have considered are motility of the GIT, difference in pH and absorption. Development of colon targeted sustained release tablet for highly water-soluble drugs has always been a difficult job because water soluble drugs, if not prepared properly and administered orally, are released at a high rate and cause problems due to toxic concentrations.[3] Hence, it is a difficult task to formulate a suitable colon targeted tablet for sustaining action of highly water- soluble drugs.[8] Hydrophilic polymers are widely used in the formulation of colon targeted sustained release oral dosage forms.[8] Different natural materials (tragacanth gum, trxanthan gum, guar gum, and chitosan) have been used by various researchers and these materials are biodegradable.[9]

It has been shown that in hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously, and both processes contribute to the overall drug release rate.[10]

HPMC k15 offers potential utility as a drug carrier because of its inertness and biocompatibility.[11] Hpmc k15 not only retards in vitro drug release and provides time independent release kinetics, but also works effectively in vivo and establishes constant drug plasma levels.[12]

Sulfasalazine is used in treatment of a certain type of bowel disease(BD) called ulcerative colitis.[13]This drug does not cure this condition, but decrease the symptoms such as inflammation, fever, stomach pain, diarrhea, and rectal bleeding.[14] The mechanism of action of Sulfasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), is not clear, but its anti-inflammatory and immunomodulatory properties have been observed in animal and in vitro models, to its affinity for connective tissue, and in high concentration it reaches in serous fluids, in the liver and intestinal walls, as established in autoradiographic studies in animals.[15] Clinical studies after rectal administration of SSZ, SP, and 5-ASA have show that this major therapeutic action in ulcerative colitis.[16] *In vivo* studies show that the absolute bioavailability of orally administered sulfasalazine is less than 15% for parent drug.[17,18] In the intestine, sulfasalazine metabolized by several intestinal bacteria to SP and 5-ASA.[19] Sulfa pyridine is relatively well absorbed from the intestine and highly metabolized, while 5-ASA is much less well absorbed.[15]

Corticosteroids are extensively used in the cureof inflammatory bowel disease (IBD).[20] Targeted of drugs to the colon is helpful in the treatment and cure of different colonic diseases

(ulcerative colitis and crohn's disease).[21] Corticosteroids are traditionally use for treating inflammatory bowel disease.[22] However chronic treatment of inflammatory bowel disease with corticosteroids, while often efficient, but this has serious side-effects (e.g. acne, moonface, hypertension, peptic ulcer and mood disturbances).[23] Steroids would have the potential of being perfect therapeutic treatments of inflammatory bowel disease.[24]

Tragacanth is a naturally occurring gum produce from Astragalus gummifer Labillardiere and other species of Astragalus.[25] The tragacanth gum consists of a mixture of water-insoluble and water-soluble poly saccharides.[9] Bassorin, which constitutes 60% to 70% of the gum,[9] is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material, tragacanth.[26] Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations.[27] It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used.[28]

The aim of this research work was to assess drug release from gum tragacanth and HPMC K15 based matrix tablet formulations of sulfasalazine and dexamethasone and the ability of these polymers in the formation of colon targeted sustained release tablets.

MATERIALS AND METHODS

Materials

Sulfasalazine and dexamethasone (AA Pharmaceuticals, Pakistan), HPMC K15 and tragacanth (Colorcon, pakistan), microcrystalline cellulose (PH 101), lactose monohydrate, Aerosil and magnesium stearate (Merck, Germany).

Preparation of matrix tablet

Preparation of matrix tablets using different proportions of HPMC K15 and tragacanth gum. Solid matrix tablets of sulfasalazine and dexamethasone were prepared using direct compression method. Sulfasalazine and dexamethasone, different proportion of HPMC K15 and tragacanth gum, Aerosil (colloidal silicon dioxide), lactose, microcrystalline cellulose (MCC) and magnesium stearate were used in preparing these matrix tablets. Developed formulations are presented in Table 1. All active and inactive ingredients were weighed individually and sieved through mesh size no. 60 and were blended for 10 min in a blender, at the end of mixing or blending Magnesium stearate 1.0% w/w was added and blended for additional 5 min. Tablets were compressed by direct compaction using multi punch machine ZP 19. The weight of tablets was adjusted to 360 mg and compressed.

Physical tests of tablets[29]

In order to determine the uniformity in weight of tablets, 20 tablets of each formulation were randomly collected and weighed using Sartorius weight balance. We find weight variation of all tablets within specification of BP 2015, result show that the filling of die cavity for tablets was uniform. All the prepared formulations were checked and the deviation was not greater than limit. The result of tablets weight variation is shown in Table 3. Hardness of tablets was also determined using curio Hardness Tester. Ten tablets of each formulation were used and the average hardness value was observed. Friability of each prepared formulation were also determined and also shown in table. Diameter and thickness of each prepared tablet also determined by using vernier calliper.

Fourier transforms infrared spectroscopy (FTIR)[30]

The 'Bruker' FTIR was used to obtain the transmittance spectrums of different polymers to check any incompatibility between the polymers used to obtain the co-processed excipients

In vitro dissolution study of sulfasalazine[31]

In vitro dissolution studies of solid matrix system *In vitro* dissolution of all the tablets was determined using the USP apparatus II, Pharma Test, China. The apparatus was validated by counting the revolutions of the paddle per minute. The test was performed in 900 mL of phosphate.

buffer (pH 6.8) with the temperature maintained at 37.0 ± 0.5˚C, while the stirring speed was maintained at 50 rpm. Samples of about 10 mL each were collected at, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours with the help of pipette. Sulfasalazine was analyzed at 358nm using spectrophotometer. Dissolution study was performed in 0.1 Hcl media for 2 hours and in phosphate buffer 7.4 pH for 3 hours, at the end tablet was checked in microbial flora with phosphate buffer of pH 6.8.

In vitro dissolution study of dexamethasone

In vitro dissolution studies of solid matrix system *In vitro* dissolution of all the tablets was determined using the USP apparatus II, Pharma Test, China. The apparatus was validated by counting the revolutions of the paddle per minute. The test was performed in 900 mL of phosphate buffer (pH 6.8) with the temperature maintained at 37.0 ± 0.50, while the stirring speed was maintained at 50 rpm. Samples of about 10 mL each were collected at, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours with the help of pipette. Dexamethasone was analyzed at 241nm using spectrophotometer. Dissolution study was performed in 0.1 Hcl media for 2 hrs and in phosphate buffer 7.4 pH for 3 hrs, at the end tablet was checked in microbial flora with phosphate buffer of pH 6.8. All the tests were run in triplicate and the average of three values were taken.

Figure 1 shows dissolution behavior of sulfasalazine in phosphate buffer (pH 7.4), 0.1 N HCl and microbial flora media (pH 6.8) for 10 h. Figure 2 indicate release profile of dexamethasone in same medium.

Kinetic modeling of drug release

Drug release shows the process of change drug in an appropriate form which could undergo the pharmacokinetic parameters (i.e. drug absorption, drug distribution, drug metabolism & excretion) & ultimately become available to produce pharmacological effect. The outcome of *in vitro* dissolution studies was applied in different mathematical models to determine the kinetics of drug release by the Sulfasalazine sustained release matrix tablets. Value of correlation co-efficient (i.e. r), derived from different mathematical models, was used to determine the model which describes the drug release from the matrix tablet system most appropriately. The zero-order kinetic model indicates the system in which independent drug release rate. In first order kinetic model, the drug release rate depends on concentration. Higuchi describes the release of the drug from an insoluble matrix as square root of time dependent process. The Hixson-Crowell cube root law indicates the drug release from a system in which there is change in the surface area and diameter of the particles present in dosage form. Korsmeyer-Peppas Equations (Diffusion/Relaxation Model) $Mt/M0 = k5t$.

First order Kinetics $Log\ Qt = (Kt/2.303) + Log\ Q0$.

Zero order Kinetics $Qt = K0\ t + Q0$.

Higuchi's release model (Diffusion model) $ft = KHt1/2$.

Equation for Korsmeyer – peppas release model $Mt/M\infty = Ktn$.

Table 1: absorbance of sulfasalazine and dexamethasone at different concentration

Sr no	concentration(mcg)	Absorbance
	Sulfasalazine	
1	10	0.696
2	14	1.046
3	20	1.500
	dexamethasone	
1	10	0.394
2	20	0.804
3	30	1.290

Table 2: Formulations with varying %age concentration of polymer and excipients

Sr.#	FORMULATION INGREDIENTS	Formulation Code								
		T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Sulfasalazine	100	100	100	100	100	100	100	100	100
2	dexamethasone	10	10	10	10	10	10	10	10	10
3	Lactose Anhydrous	101.4	101.4	101.4	84	84	84	66.5	66.5	66.5
4	MCC	56	56	56	56	56	56	56	56	56
5	Magnesium Stearate	5	5	5	5	5	5	5	5	5
6	Tragacanth Gum	43.8	22	14.6	52.5	26.25	17.5	61.25	30.63	20.42
7	HPMC K15	43.8	65.63	73	52.5	78.75	87.5	61.25	91.9	102.08
	TOTAL	360 mg	360 mg	360 mg	360 mg	360 mg	360 mg	360 mg	360 mg	360 mg

Table 3: various physical tests performed on the tablet formulations

Trial No.	Diameter (mm)	Thickness (mm)	Hardness Kg/cm^2	Friability (%)	Weight Variation (%)
T1	10.64 ± 0.0133	4.22 ± 0.1188	6.75 ± 0.991	0.25	1.2
T2	10.65 ± 0.0233	4.43 ± 0.0911	7.52 ± 0.221	0.61	2.3
T3	10.62 ± 0.0066	4.24 ± 0.0988	6.82 ± 0.921	0.35	1.4
T4	10.63 ± 0.0033	4.26 ± 0.0788	6.94 ± 0.801	0.47	0.71
T5	10.62 ± 0.0066	4.28 ± 0.0588	8.34 ± 0.598	0.51	1.4
T6	10.61 ± 0.0166	4.50 ± 0.1611	7.24 ± 0.501	0.57	0.25
T7	10.63 ± 0.0033	4.48 ± 0.1411	8.36 ± 0.618	0.29	1.1
T8	10.620. ± 0066	4.26 ± 0.0788	9.5 ± 1.758	0.61	1.7
T9	10.62 ± 0.0066	4.38 ± 0.0411	8.2 ± 0.458	0.37	2.1

Table 4: Assay (percentage drug content in various formulations)

Trial No.	Assay of Dexamethasone	Assay of Sulfasalazine
T1	97.2	98.3
T2	102.4	101.6
T3	103.1	97.1
T4	101.7	103.2
T5	102.5	101.5
T6	104.4	102.2
T7	99.8	98.2
T8	103.5	103.9
T9	104.2	103.1

Table 5: release profile (sulfasalazine) of various tablet formulation

Time (hr)	0	1	2	3	4	6	8	10	12
T1	0	31.99	49.23	57.79	97.87	-	-	-	-
T2	0	32.74	48.82	55.31	50.23	71.95	80.73	94.25	-
T3	0	35.03	47.73	51.24	63.86	87.15	95.74	-	-
T4	0	36.76	54.05	61.93	80.4	93.68	-	-	-
T5	0	25.72	31.95	38.66	65.94	74.62	87.8	98.61	-
T6	0	24.86	36.28	38.17	50.23	65.02	91.02	95.37	100
T7	0	29.49	40.91	42.82	49.24	69.65	95.65	-	-
T8	0	21.15	41.04	49.04	65.94	75.08	86.18	98.96	100
T9	0	11.16	30.9	47.99	59.24	71.1	78.11	85.06	97.7

Table 6: Release profile (dexamethasone) of various tablet formulation

Time (hr)	0	1	2	3	4	6	8	10	12
T1	0	22.0	39.23	47.29	97.87	-	-	-	-
T2	0	31.32	39.22	45.31	50.23	71.95	80.73	-	-
T3	0	25.03	37.23	41.24	63.86	87.15	-	-	-
T4	0	26.76	44.05	64.43	80.4	93.68	-	-	-
T5	0	15.72	29.25	48.36	45.44	84.62	-	-	-
T6	0	34.86	46.28	38.37	46.23	65.02	83.43	-	-
T7	0	21.49	30.91	42.83	49.24	69.65	85.65	-	-
T8	0	13.15	21.04	49.04	65.94	75.08	86.18	-	-
T9	0	11.26	20.9	37.49	49.24	61.32	78.11	85.06	-

Table 7: Blend flow properties of pre compressed powder

Sr. no.	Formulation trial no.	Angle of repose(θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio
1	T1	28.72	0.618	0.761	18.75	1.23
2	T2	26.35	0.649	0.769	15.63	1.19
3	T3	27.12	0.610	0.697	12.50	1.14
4	T4	25.24	0.721	0.781	7.69	1.08
5	T5	29.36	0.636	0.749	15.15	1.18
6	T6	29.64	0.668	0.713	6.25	1.07
7	T7	28.74	0.659	0.727	9.38	1.10
8	T8	25.92	0.625	0.708	11.76	1.13
9	T9	26.58	0.646	0.711	9.09	1.10

Table 8: Kinetic modeling of *in vitro* dissolution data all trial formulations (sulfasalazine)

Formulation	pH	Zero order release kinetics		First order release kinetics		Higuchi model	
		K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_2 (h^{-1})	r^2
T5	1.2	9.962	0.965	-0.259	0.986	0.38	0.963
	6.8	9.962	0.965	0.022	0.03	0.364	0.99
	7.4	10.86	0.99	0.022	0.03	0.392	0.992
T7	1.2	10.51	0.956	-0.259	0.986	0.380	0.963
	6.8	9.962	0.965	-0.446	0.986	0.364	0.990
	7.4	10.867	0.990	0.022	0.030	0.392	0.992
T8	1.2	12.959	0.898	-0.014	0.004	0.473	0.920
	6.8	8.933	0.753	-0.999	0.992	0.348	0.879
	7.4	10.042	0.908	0.024	0.009	0.374	0.972

Table 9: Korsemeyer–peppas model of *in vitro* dissolution data of the trial (sulfasalazine)

Formulation	pH	Korsemeyer –peppas model		Mechanism of Drug transport
		Release exponent 'n'	r^2	
T5	1.2	0.8	0.965	Non- Fickian diffusion
	6.8	0.543	0.991	Non- Fickian diffusion
	7.4	0.614	0.994	Non- Fickian diffusion
T7	1.2	0.800	0.966	Non- Fickian diffusion
	6.8	0.543	0.992	Non- Fickian diffusion
	7.4	0.614	0.995	Non- Fickian diffusion
T8	1.2	0.877	0.929	Non- Fickian diffusion
	6.8	0.50	0.942	Non- Fickian diffusion
	7.4	0.50	0.983	Non- Fickian diffusion

Table 10: Kinetic modeling of *in vitro* dissolution data dexamethasone

Formulation	pH	Zero order release kinetics		First order release kinetics		Higuchi model	
		K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_2 (h^{-1})	r^2
T7	1.2	9.806	0.96	-0.217	0.979	0.35	0.944
	6.8	8.689	0.998	-0.208	0.972	0.308	0.967
	7.4	8.923	0.973	-0.215	0.993	0.323	0.983

Table 11: Korsemeyer–peppas model of *in vitro* dissolution data of dexamethasone

Formulation	pH	Korsemeyer –peppas model		Mechanism of Drug transport
		Release exponent 'n'	r^2	
T7	1.2	0.80	0.964	Non- Fickian diffusion
	6.8	0.533	0.951	Non- Fickian diffusion
	7.4	0.634	0.944	Non- Fickian diffusion

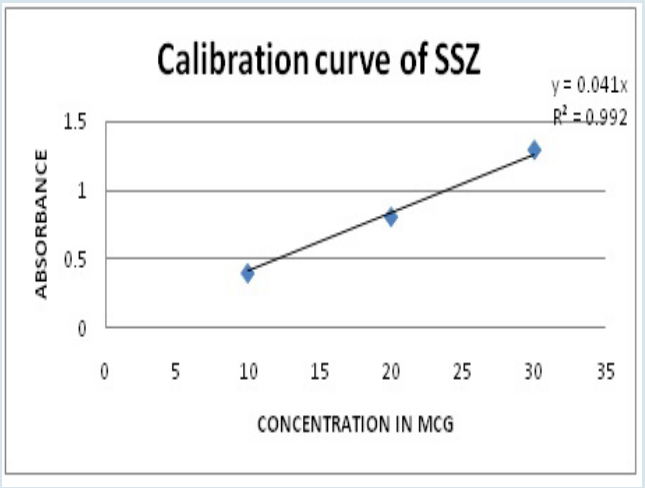

Figure 1: calibration curve of sulfasalazine0.

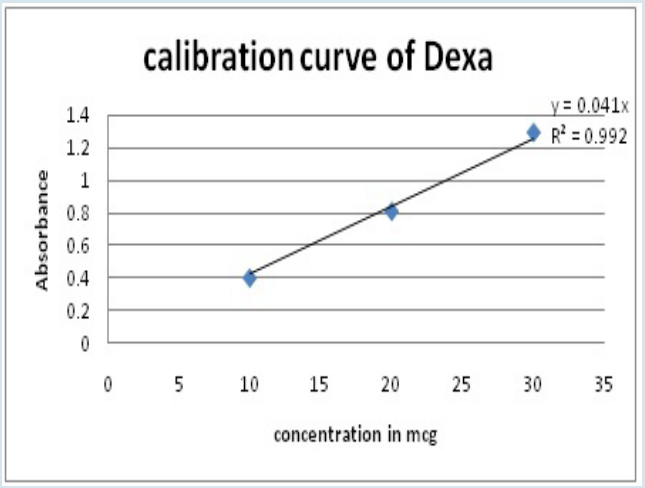

Figure 2: calibration curve of dexamethasone.

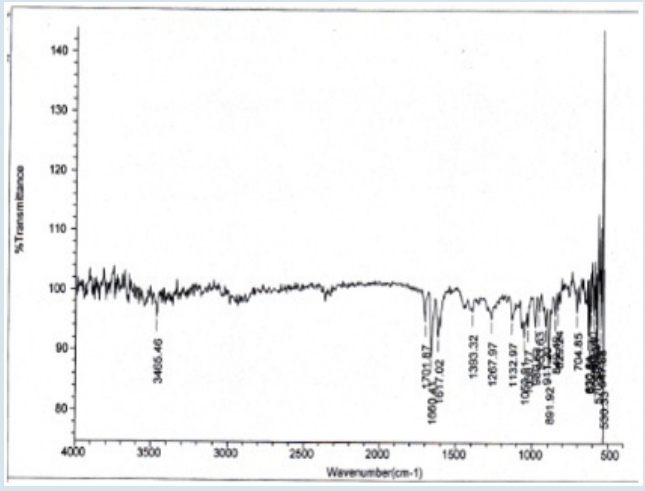

Figure 3: FTIR of Dexamethasone.

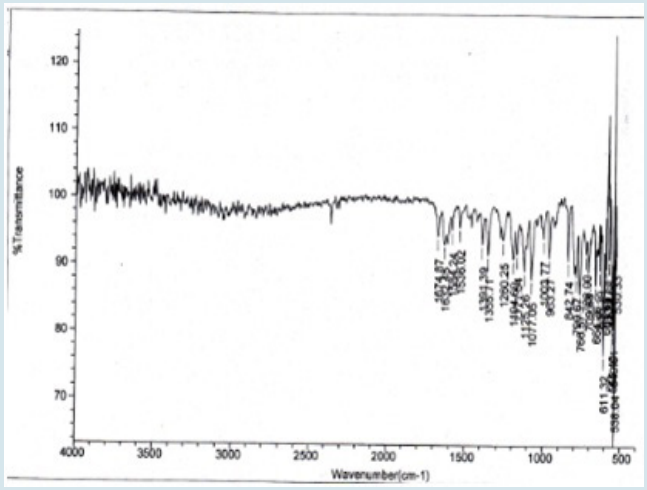

Figure 4: FTIR of sulfasalazine.

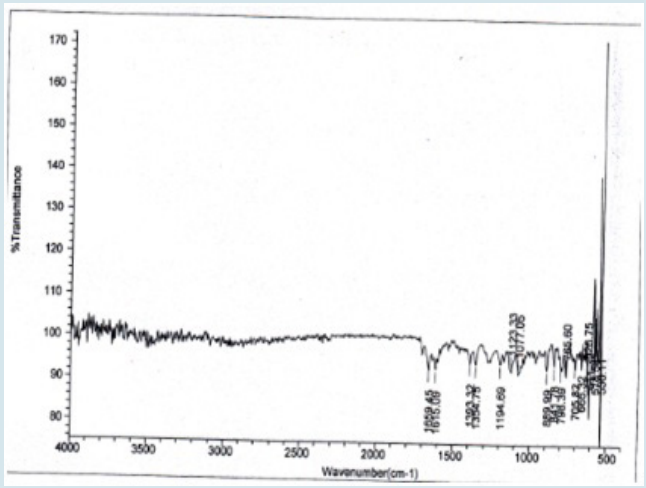

Figure 5: FTIR of blend.

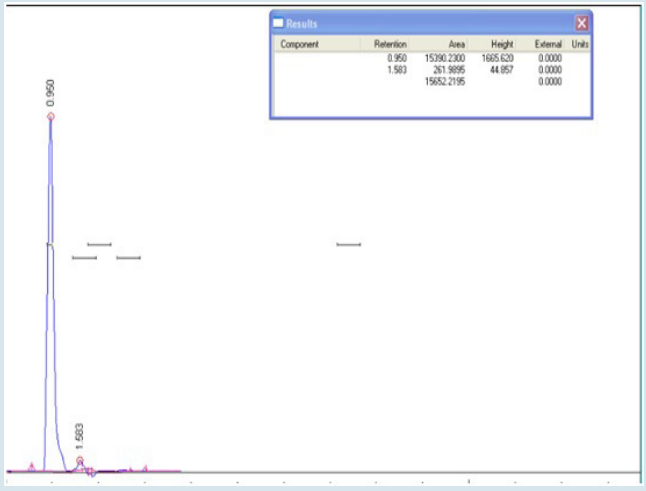

Figure 6: HPLC of dexamethasone sodium.

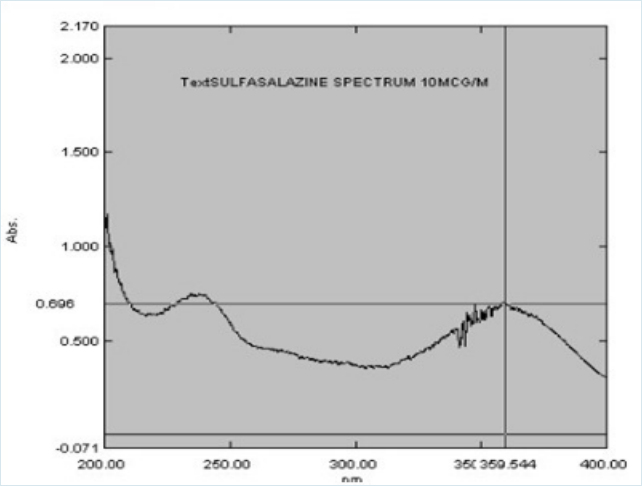

Figure 7: UV spectrum of sulfasalazine.

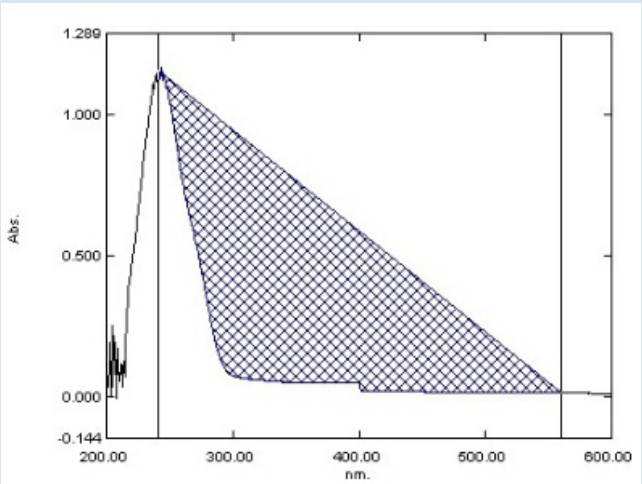

Figure 8: UV spectrum of dexamethasone.

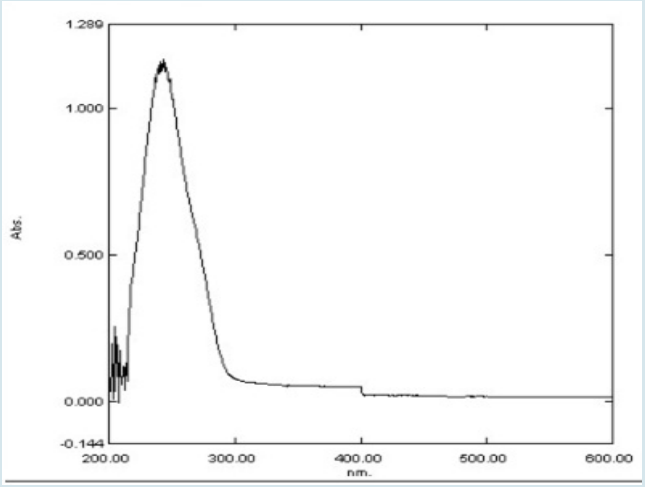

Figure 9: UV spectrum of dexamethasone.

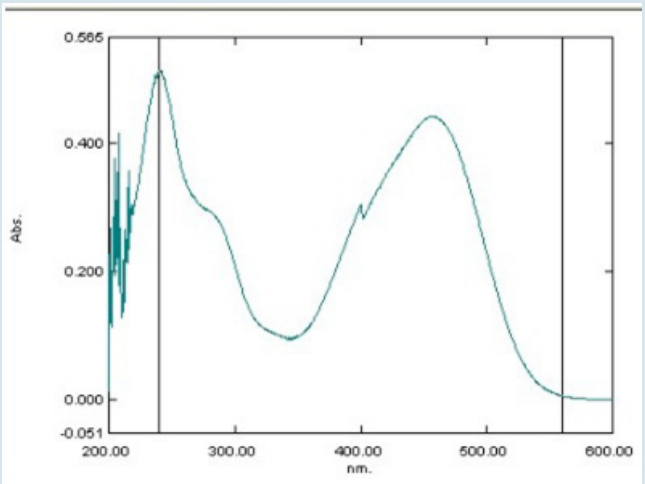

Figure 10: UV spectrums of sulfasalazine and dexamethasone.

RESULTS AND DISCUSSION

FTIR spectroscopy is a simple and quick technique to identify any chemical changes or interaction. FTIR spectra of active, HPMC k15, tragacanth gum and excipients made by their co-processing with their respective peaks have been shown in the Figure 3, 4 and 5. FTIR spectra of blend indicated absence of any chemical interaction. Figure 6 show the HPLC peak of dexamethasone. Table 5 show release data of all formulations concerning sulfasalazine and Table 6 show release profile of dexamethasone.

Kinetic modeling of sulfasalazine and dexamethasone.

Regression coefficient R^2 were determined by mathematical models of release kinetics by incorporating data of 10-12 hours release of two formulations which have best result and release constant k was also determined by slope of graph. To evaluate the drug release mechanism first order, zero order, Hixson Crowell Equation, Higuchi model & korsmeyer model were used. T5 and T7 and T8 formulations (sulfasalazine) followed zero and Higuchi model in the pH7.4 buffer indicate the release of drug was through diffusion. Table 8 and 9 show kinetic modeling of sulfasalazine and Table 10 and 11 shows the kinetic profile of dexamethasone.

Calibration Curve

The calibration curve of sulfasalazine in 0.1N HCl (pH 1.2), phosphate buffer of pH 6.8 and pH 7.4 using U.V. spectrophotometer at 359 nm for sulfasalazine and 241 for dexamethasone. Figure 1 and 2 show regression of both active ingredients.

DISCUSSION

Colon targeted Matrix tablets of sulfasalazine and dexamethasone using mixture of semi synthetic and natural polymers are formulated with direct compression technique. Post-compression parameters were checked and were found to be within limits. FTIR indicated there is no considerable interaction or alteration in the structure. We compared different prepared formulations. The results of *in vitro* dissolution in pH 6.8 buffer showed that trial formulations T6, T8 & T9 exhibited more sustained release in comparison to other formulations. Since tragacanth gum is soluble above pH 6.0 so it was dissolved immediately in pH 6.8 buffer. So the retardation of drug release was only depended upon the matrix formation by HPMC K15. So the prepared formulations, having higher

content of HPMC K15 polymer, exhibited more sustained release over the period of 8 hours e.g., Trial T2, T5 & T7 had showed a drug release of 50.23, 65.94 & 49.24% respectively after 4 hours. While the prepared formulation T1 having the least amount of HPMC K15 showed the highest drug release of 97.87% after 4 hrs. Hence the trial T9 having maximum percentage content of HPMC K15 so retarded the drug release most efficiently for 8 hrs. The dissolution results after 4 hrs in pH 6.8 (with microbial flora) buffers for T2, T4 & T7 were 71.36%, 65.94% & 49.24% respectively. Results shown that increasing the percentage of polymer in the trial decreased the drug release proportionally. The formulation T7 having the 1:1 ratio of HPMC K15 & tragacanth gum, also gives the most sustained drug release.

CONCLUSION

This study was started with the aim of developing matrix release tablet of Sulfasalazine and dexamethasone in combination form for the colon. The final formulation powder blends containing polymer and excipients which exhibited good flow properties and no problem was encountered during the compression of tablets. The physical tests performed on the tablets showed acceptable results. Hence the direct compression method was satisfactorily applied for the production of tablets. The whole study concluded into an optimized formulation of T7 which exhibited good sustained drug release for a time period of 8 hours. Trial formulation T7 had 61 mg of HPMC k15 and 61 mg of tragacanth with a ratio of 1:1.

So it can be finally stated that the usage of natural polymer i.e., tragacanth gum and semi synthetic polymer HPMC k15 & application of direct compression method resulted into a comparatively economical sustained release tablets of Sulfasalazine and dexamethasone which can lead to enhanced patient compliance

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CONFLICT OF INTEREST

No conflict of interest.

ABBREVIATIONS USED

MCC: Microcrystalline cellulose; **SSZ:** Sulfasalazine; **HPMC k15:** Hydroxypropyl methylcellulose k15.

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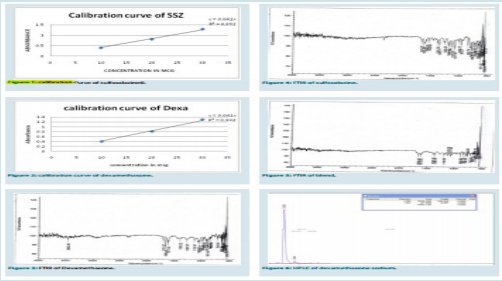
PICTORIAL ABSTRACT



SUMMARY

- The aim of this research work was to assess drug release from gum tragacanth and HPMC K15 based matrix tablet formulations of sulfasalazine and dexamethasone and the ability of these polymers in the formation of colon targeted sustained release tablets.
- Sulfasalazine is used in treatment of a certain type of bowel disease(BD) called ulcerative colitis.
- Corticosteroids are extensively used in the cure of inflammatory bowel disease (IBD).
- Tragacanth is a naturally occurring gum produce from Astragalus gummifer Labillardiere and other species of Astragalus

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Yasir Mehmood: Is working as Quality Control Manager in National pharmaceutical industry. His current research interests are formulation development of different dosage form, clinical study design and different health related issues. He is also reviewer and editorial member of some journals.