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DEVELOPMENT AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF MONTELUKAST SODIUM

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ABSTRACT

In the present study an attempt has been made to develop and formulate controlled release gastroretentive floating tablets of montelukast Sodium by using HPMC K100M, xanthan gum, guar gum as drug release retardants. Montelukast sodium is a leukotriene receptor antagonist (LTRA) administered as oral tablets at high doses 2-3 times per day. Hence in the present investigation, it is aimed to develop effervescent floating tablets of montelukast inorder to reduce frequency of dosing, achieve maximum gastric residence time and to improve drug availability. The tablets were evaluated for physical properties including hardness, weight variation, thickness, friability, drug content. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were evaluated for post compression parameters such as hardness, thickness, friability, percent drug content, weight variation tests and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F11 formulation with HPMC K100M, ethyl cellulose and sodium bicarbonate as gas generating agent provides the 99.32 % of drug release up to 12hours. The drug release from the optimized formulation followed both zero order and Higuchi kinetics. The results of the present study ccludes that gastroretentive floating tablets for montelukast were successfully formulated by using different grades of hydrophilic polymers such as HPMC K100, xanthan and guargum.

KEYWORDS: Montelukast, HPMC K100M, xanthan gum, guar gum, gastroretentive floating tablets.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Controlled drug delivery results in optimum therapy, and not only reduces the frequency of dosing, but may also reduce the severity and frequency of side effects.[1,2,3] The de novo design of oral controlled drug delivery systems should primarily be aimed at achieving more predictable and increased bioavailability of drugs. However, the developmental process is precluded by several physiological difficulties, such as inability to restrain and locate the controlled drug delivery systems within desired regions of gastrointestinal tract due to the variable gastric emptying and motility.

Gastric floating drug delivery systems (GFDDS)

Gastric floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolonged period. The need for gastric retention dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems in which the problems associated with oral controlled release dosage forms could be rectified to a satisfactory extent for drugs having site-specific absorption at stomach or upper parts of small intestine.[4]

MATERIALS AND METHODS

Materials used for the formulation development

Montelukast Sodium, HPMC K 100 M, Xanthan gum, Guar gum, Ethyl cellulose, Sodium bicarbonate, Citric acid, Lactose, Magnesium stearate and Talc.

RESULTS AND DISCUSSION

Table 1: Composition of Formulation table for montelukast sodium

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Montelukast	10	10	10	10	10	10	10	10	10	10	10	10
Xanthan gum	15	20	25	30	-	-	-	-	-	-	-	-
Guar gum	-	-	-	-	15	20	25	30	-	-	-	-
HPMC K 100 M	-	-	-	-	-	-	-	-	15	20	25	30
Ethyl cellulose	20	20	20	20	20	20	20	20	20	20	20	20
$NaHCO_3$	10	10	10	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
MCC	50	50	50	50	50	50	50	50	50	50	50	50
Starch	36	31	26	21	36	31	26	21	36	31	26	21
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Calibration curve for the estimation of Montelukast in 0.1N HCl

S. No	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.124
3	10	0.242
4.	15	0.323
5.	20	0.402
6.	25	0.539
7.	30	0.654

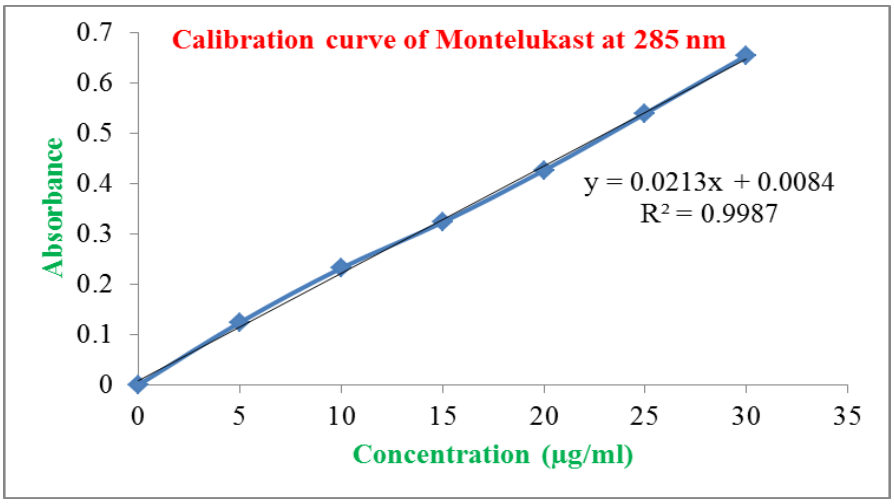

Figure 1: Standard plot of Montelukast at 285 nm

Table 3: Physical parameters of the precompression blend

Formulation	Compressibility Index	Angle of repose	Hausner ratio
F1	13.25±0.34	22.25±0.12	1.18±0.82
F2	18.59±0.12	21.16±0.31	1.38±0.54
F3	15.52±0.14	36.52±0.93	1.24±0.78
F4	17.86±0.25	28.56±0.34	1.18±0.56
F5	14.29±0.32	22.85±0.67	1.23±0.38
F6	17.84±0.54	21.43±0.89	1.16±0.32
F7	19.58±0.43	23.45±0.41	1.32±0.93
F8	15.56±0.61	22.47±0.62	1.16±0.26
F9	14.78±0.28	26.89±0.64	1.15±0.46
F10	17.42±0.32	27.45±0.15	1.27±0.62
F11	18.56±0.36	22.51±0.41	1.35±0.39
F12	14.28±0.53	21.85±0.62	1.26±0.20

Table 4: Evaluation of post compression parameters

Batch No.	Average weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	148.23±0.72	4.23±0.271	0.20	99.1
F2	149.62±0.56	4.61±0.268	0.12	99.7
F3	150.71±0.76	4.52±0.36	0.18	98.23
F4	149.25±1.42	4.73±0.361	0.16	99.62
F5	151.43.±0.96	4.76±0.213	0.13	97.27
F6	150.70±0.37	5.85±0.301	0.23	99.5
F7	148.52±0.18	4.88±0.310	0.20	101.4
F8	149.96±1.21	4.52±0.213	0.19	97.9
F9	150.95±1.32	4.36±0.403	0.20	98.8
F10	149.91±1.44	4.95±0.415	0.18	99.97
F11	151.84±1.51	4.11±0.353	0.18	99.2
F12	148.77±1.67	5.17±0.347	0.17	101.2

Table 5: In Vitro Buoyancy results of prepared formulations

Formulation	Floating lag time (Sec)	Total floating time (Hrs.)
F1	80 Sec	8
F2	60 Sec	7
F3	50 Sec	8
F4	60 Sec	>12
F5	1 min 3 Sec	8
F6	3 min 10 sec	6
F7	45 Sec	7
F8	2 min 5 sec	5
F9	80 sec	10.5
F10	40 Sec	>12
F11	30 Sec	>12
F12	1 min 6 Sec	>12

Table 6: Cumulative % release of formulations F9-F12 & Pure Drug

Time (hrs)	F9±SD	F10 ±SD	F11±SD	F12±SD
0.25	13.47±0.47	10.96±0.65	5.87±1.52	3.76±0.32
0.50	20.34±0.45	19.32±0.84	15.25±1.92	9.86±0.58
0.75	36.87±0.95	32.02±0.94	28.45±0.48	20.67±0.88
1	40.08±0.45	39.98±0.97	36.99±0.82	29.97±0.93
2	63.90±0.62	58.04±0.76	45.94±0.46	32.45±0.48
4	78.56±0.72	69.43±0.49	58.54±0.59	39.66±0.77
6	84.96±0.23	79.67±0.39	69.09±0.93	49.76±0.29
8	96.29±0.54	85.0±0.59	76.86±0.49	59.12±0.71
10	---	97.03±0.98	89.02±0.58	67.34±0.52
12	---	---	99.32±0.69	75.56± 0.95

Table 7: Drug release kinetics of prepared floating formulations

Formulation	Correlation Co-efficient (r) value				Korsemeyer - Peppas	
	Zero order	First order	Higuchi's	Erosion	r value	n value
F1	0.744	0.983	0.596	0.733	0.984	0.353
F2	0.835	0.97	0.613	0.826	0.853	0.345
F3	0.863	0.936	0.615	0.855	0.954	0.441
F4	0.891	0.894	0.709	0.886	0.911	0.630
F5	0.703	0.946	0.638	0.698	0.441	0.558
F6	0.759	0.949	0.590	0.826	0.921	0.427
F7	0.899	0.952	0.694	0.893	0.973	0.549
F8	0.903	0.924	0.703	0.898	0.925	0.569
F9	0.840	0.967	0.671	0.834	0.943	0.556
F10	0.850	0.935	0.667	0.844	0.935	0.547

F11	**0.901**	**0.873**	**0.705**	**0.896**	**0.900**	**0.615**
F12	0.912	0.971	0.734	0.906	0.883	0.646
Pure Drug	0.84	0.730	0.700	0.921	0.986	0.311

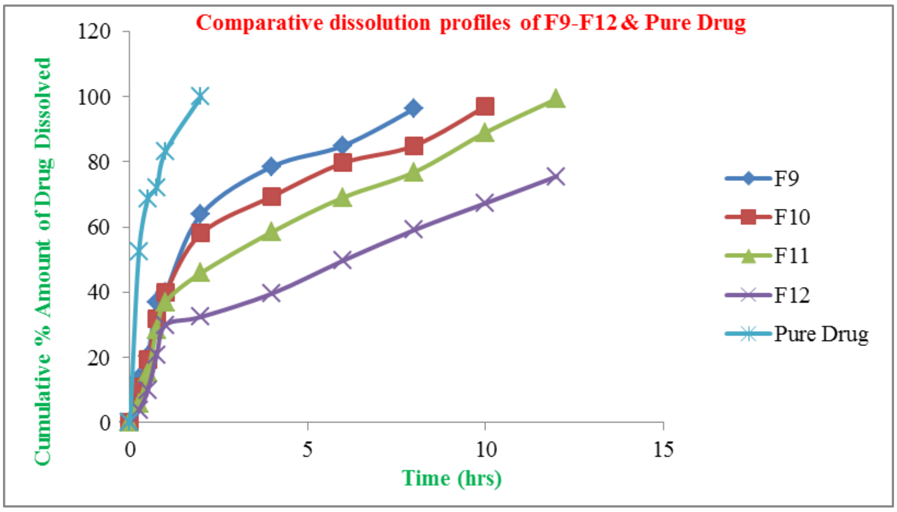

Figure 2: Comparative dissolution profiles of F9-F12 & Pure Drug

Formulations F9, F10, F11 and F12 were prepared by employing HPMC 100 K with different polymer proportions. F9 had shown 96.29% in 8 hours, F10 had shown 97.03% in 10 hours, F11 had shown 99.32% in 12 hours and F12 formulation had shown 75.56% drug release in 12 hours. It indicates that F9, F10, formulations which contains HPMC 100 K failed to retard the drug release up to 12 hours. But F11 formulation has retarded the drug release up to 12 hours with less floating lag time and it was observed that floating duration was more than 12 hours. F12 formulation had shown 75.56 % drug release for 12 hours. It indicates that as the concentration of polymer increases the drug release was decreased (Table 6, figure 2).

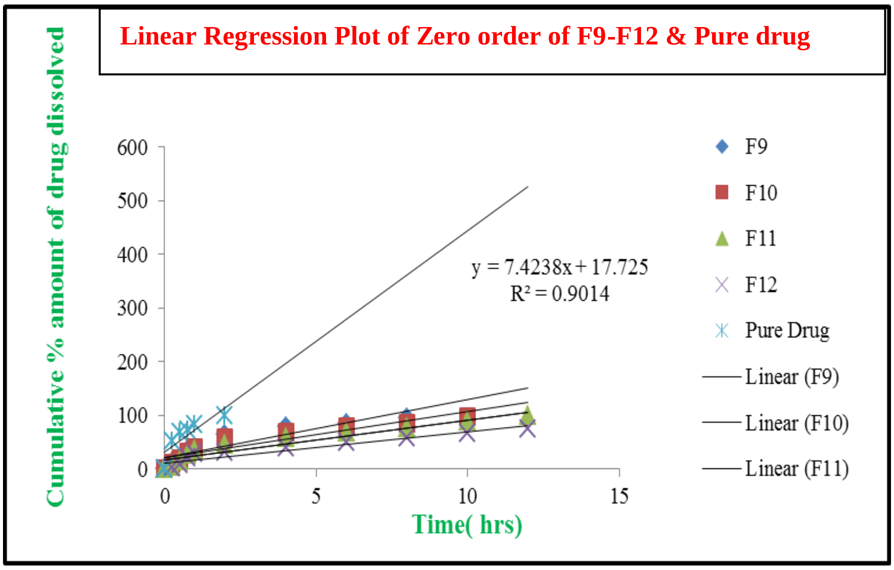

Figure 3: Linear regresion plots of zero order of F9-F12 &Pure drug

The drug release of GFDDS prepared from HPMCK100M of F11 formulation followed zero order kinetics, which is indicated by r values of zero order release model (0.901), slightly higher when compared to those of first order release model (0.873).

The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and erosion model. It was found that diffusion (0.705) as well as erosion (0.896) governs the drug release from these formulations as indicated by r values (Table 7, figure 3).

Though the drug release is governed by diffusion as well as erosion, the contribution of drug matrix erosion is found to be slightly higher than that of diffusion as indicated by the higher r values of erosion model. It can be concluded that the drug release is predominately governed by erosion rather than diffusion. From this, it is clearly evident that the increase in the polymer content in the GFDDS decreased the dissolution rate of drug.

When the release data were analyzed as per peppas equation, the release exponent ‘n’ for F11 formulation was >0.5 to <1 with all the formulations indicating Non Fickian Diffusion as the release mechanism.

Drug-polymer compatibility studies

IR spectroscopic studies

No prominent difference was observed in the IR peaks of Montelukast + HPMC 100 K physical mixtures and optimized formulations upon comparison with the peaks of drug and polymer alone, which may considered that Montelukast and HPMC K100M are compatible enoughwithout any interactions (figure 4, 5).

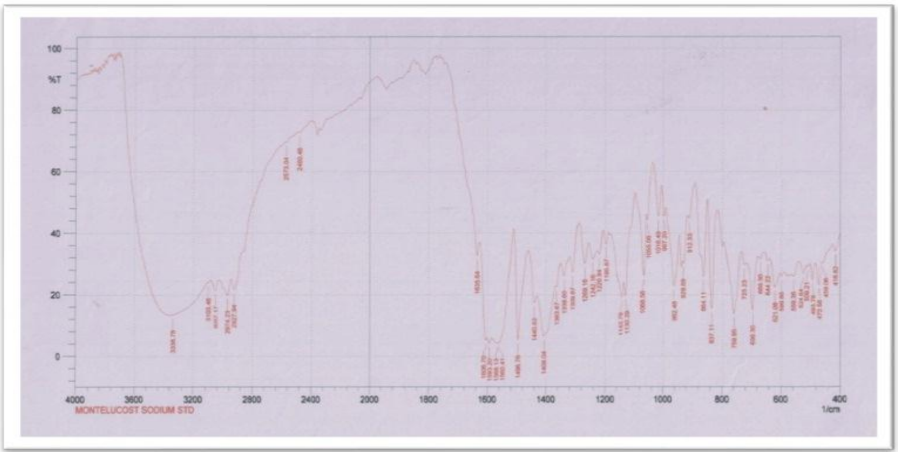

Figure 4: IR Spectrum of Montelukast pure drug

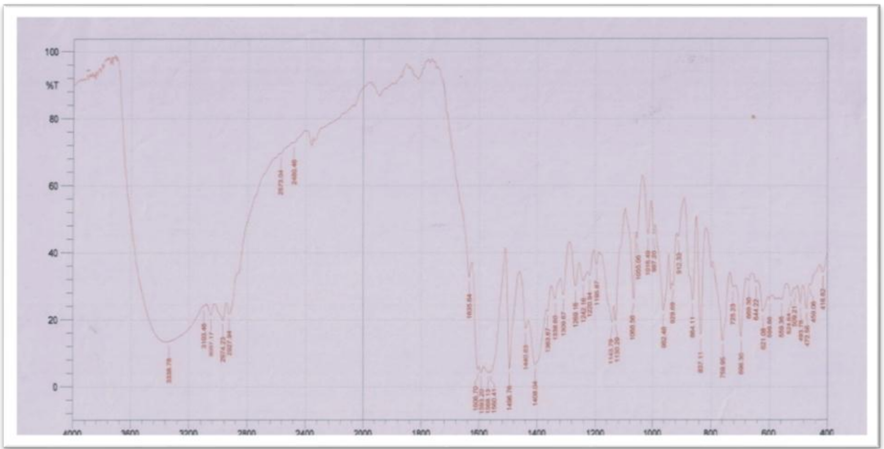

Figure 5: IR Spectrum of Montelukast and HPMC K 100 M physical mixture

CONCLUSION

In the present investigation, GFDDS of montelukast were developed with hydrophilic polymers like HPMC K100M, xanthan gum and guar gum to deliver montelukast to the upper parts of the small intestine in a controlled manner to improve its bioavailability. The GFDDS of montelukast were developed in the form of tablets comprising of an effervescent agent.

The dissolution data were fitted to four popular release models such as zero-order, first-order, diffusion and erosion equations to determine the release mechanism. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. The results of the present study thus clearly indicated that GFDDS for montelukast were successfully formulated by using different grades of hydrophilic polymers such as HPMC K100, xanthan and guargum. From the results it can be concluded that F11 with HPMC K100M, ethyl cellulose and sodium bicarbonate as gas generating agent provides the 99.32 % of drug release up to 12hours.

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