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FORMULATION AND INVITRO EVALUATION OF MISOPROSTOL NON -EFFERVESCENT FLOATING TABLETS

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Abstract : In the present research work non effervescent floating matrix formulation of Misoprostol by using various polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Floating agent accurel concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural and synthetic polymers. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Methocel K15 were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with karaya gum retarded the drug release up to 12 hours in the concentration of 7.5 mg (F6).The formulations prepared with Sodium CMC were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

Keywords: Misoprostol, Sodium CMC, Methocel K15 M and Non effervescent Floating tablets.

Introduction

Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them. FDDS are hydro-dynamically controlled low-density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The residual system is emptied from the stomach with the release of the drug. This results in enhanced gastric residence time and good control over plasma drug concentration fluctuations. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Prolonging the gastric retention of a delivery system is desirable for achieving the greater therapeutic efficacy of the drug substance under certain circumstances. For example, drugs which show better absorption at the proximal part of the gastrointestinal tract and drugs with low solubility and get degraded in alkaline pH found efficient in prolonging gastric retention. In addition, for sustained drug delivery to the stomach and proximal small intestine in treating certain ulcerative conditions, prolong gastric retention of the therapeutic moiety and hence offer numerous advantages including improved bioavailability and therapeutic efficacy with reduction of dosing frequency

Materials and Methods

Misoprostol, karayagum,methocel K 100M, Sodium CMC Accural, Micro crystalline cellulose, Magnesium stearate, Talc all the chemicals used were laboratory grade.

Formulation (Or) Preparation of Floating Tablets Of Misoprostol

Optimization of Accural concentration:

Accural was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of Accural were employed; floating lag time and floating duration were observed. Based on that the concentration of Accural was finalised and preceded for further formulations.

Optimization Accural concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Misoprostol	0.200	0.200	0.200
2	Methocel K15 M	5	5	5
4	Accurel	2.5	5	7.5
5	Mg.Stearate	3	3	3
5	Talc	3	3	3
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	60	60	60

All the quantities were in mg.

Formulation composition for floating tablets

Formulation No.	Misoprostol	Methocel K 100 M	Karaya gum	Sodium CMC	Accurel	Mag. Stearate	Talc	MCC pH 102
F1	0.200	2.5	-----	-----	5	3	3	QS
F2	0.200	5	-----	-----	5	3	3	QS
F3	0.200	7.5	-----	-----	5	3	3	QS
F4	0.200	-----	2.5	-----	5	3	3	QS
F5	0.200	-----	5	-----	5	3	3	QS
F6	0.200	-----	7.5	-----	5	3	3	QS
F7	0.200	-----	-----	2.5	5	3	3	QS
F8	0.200	-----	-----	5	5	3	3	QS
F9	0.200	-----	-----	7.5	5	3	3	QS

All the quantities were in mg, Total weight is 60 mg.

Method of Preparation:

All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 3.7.The tablets were prepared as per the procedure given below and aim is to prolong the release of Misoprostol. Total weight of the tablet was considered as 60mg.

Procedure:

1) Misoprostol and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets

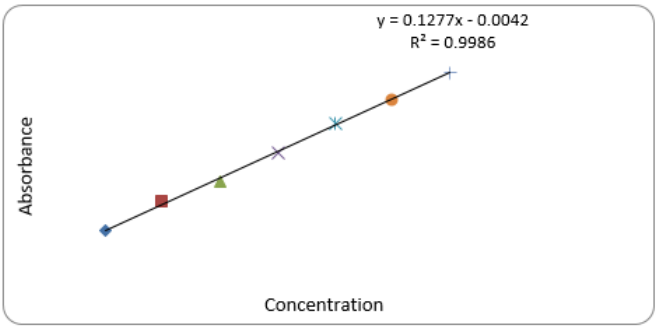
The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Results and Discussion

Standard Graph of Misoprostol in 0.1N HCl at 261nm:

The standard graph values of Terfenadine are tabulated as below-

Conc [µg/l]	Abs
1	0.131
2	0.232
3	0.377
4	0.519
5	0.629
6	0.764



Standardgraph of misoprostol

Precompression Evaluation Parameters Of misoprostol Floating Formulation Blend:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder

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blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.45 to 0.55 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.55 to 0.67 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties.All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties

Micromeritic properties of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.65	0.45	0.63	17.45	0.72
F2	23.21	0.52	0.56	17.23	1.17
F3	26.13	0.55	0.59	16.67	1.09
F4	23.45	0.48	0.61	16.32	0.83
F5	24.32	0.51	0.65	17.13	0.43
F6	25.09	0.47	0.61	16.65	0.67
F7	23.87	0.56	0.55	17.34	1.16
F8	26.42	0.51	0.57	16.33	0.49
F9	25.12	0.53	0.67	16.43	0.98

Post Compression Evaluation Parameters Of misoprostol, floating Tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	64.78	3.4	0.49	3.7	99.65	4.5
F2	59.32	3.5	0.55	3.5	98.32	4.1
F3	63.12	3.1	0.51	4.3	99.76	4.4
F4	66.76	3.3	0.48	3.4	98.55	4.2
F5	60.18	3.2	0.5	3.9	99.43	4.3
F6	58.07	3.4	0.52	4.8	98.87	4.6
F7	69.54	3.5	0.54	4.5	99.23	4.5
F8	67.31	3.1	0.43	3.8	99.13	4.1
F9	62.56	3.3	0.52	3.6	99.58	4.3

. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

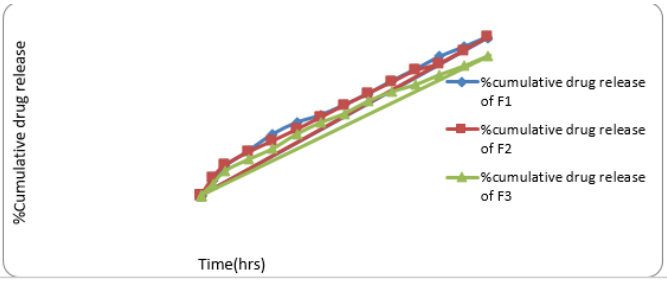
Invitro Drug Release Studies

Dissolution Data of Misoprostol Tablets Prepared with Karaya gum in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0.5	8.24	9.76	6.36
1	15.76	16.35	13.24
2	24.35	23.52	19.63
3	33.25	29.46	25.35
4	39.51	35.63	33.18
5	43.52	42.13	39.45
6	49.09	48.65	44.35
7	55.13	55.1	51.14
8	62.15	61.24	56.25
9	68.45	67.54	60.13
10	75.29	71.22	65.53
11	80.42	78.34	70.09
12	85.31	85.44	75.34

DISSOLUTION PROFILE OF MISOPROSTOL FLOATING TABLETS (F1,F2,F3 FORMULATIONS)

Dissolution Data of Misoprostol Tablets Prepared With Methocel K100Min Different Concentrations



TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F4	F5	F6
0.5	8.45	3.78	9.35
1	15.35	9.13	17.18
2	24.98	18.64	25.63
3	31.87	25.74	32.25
4	38.43	32.26	38.65
5	43.41	39.36	45.31
6	49.65	46.18	53.42
7	55.38	52.44	60.04
8	62.13	61.28	67.43
9	68.4	70.34	73.39
10	72.54	78.46	79.06
11	79.64	85.63	87.32
12	84.19	93.09	98.55

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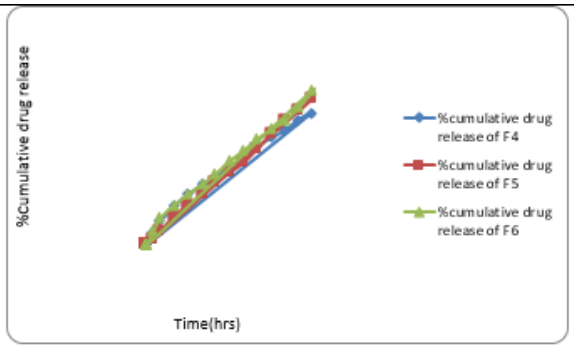
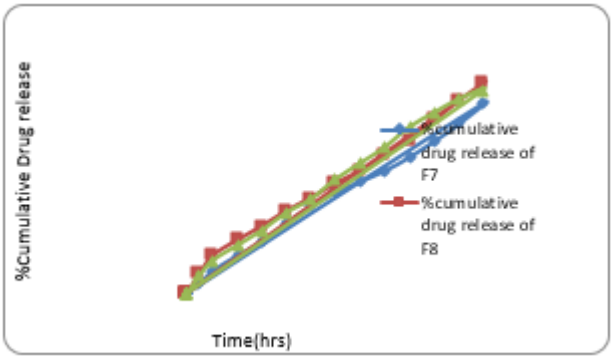


TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0.5	3.87	8.53	7.63
1	9.46	16.36	14.13
2	16.35	23.34	20.84
3	22.43	29.5	27.46
4	30.76	36.41	35.35
5	38.39	42.1	41.31
6	44.64	48.67	50.07
7	Chart Area	54.19	57.22
8	54.13	61.12	64.23
9	60.24	67.47	73.21
10	67.29	76.34	79.56
11	75.08	85.24	85.53
12	84.42	93.09	89.59



Dissolution profile of Misoprostol floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulationsprepared with Karaya gum retarded the drug release in the concentration of 7.5 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.55 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time.

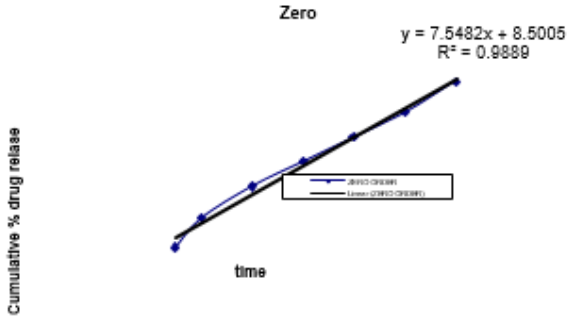
The formulations prepared with Methocel K100M and Sodium CMC showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

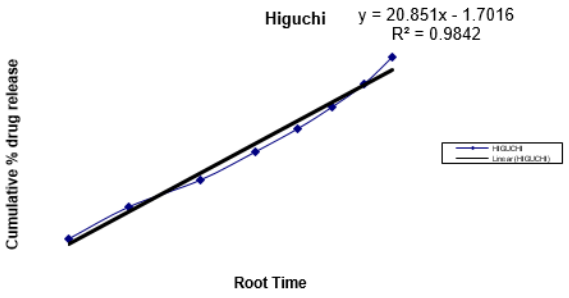
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
	0	0			2.000
9.35	0.5	0.458	0.971	1.987	1.957
17.18	1	1.000	1.235	0.000	1.918
25.63	2	1.414	1.409	0.301	1.871
32.25	3	1.732	1.372	0.477	1.883
38.65	4	2.000	1.587	0.602	1.788
45.31	5	2.236	1.587	0.699	1.788
53.42	6	2.449	1.656	0.778	1.738
60.04	7	2.646	1.728	0.845	1.668
67.43	8	2.828	1.778	0.903	1.602
73.39	9	3.000	1.829	0.954	1.513
79.06	10	3.162	1.866	1.000	1.425
87.32	11	3.317	1.898	1.041	1.321
98.55	12	3.464	1.941	1.079	1.103

Release kinetics data for optimised formulation (F6)



Zero order release kinetics graph



Higuchi release kinetics graph

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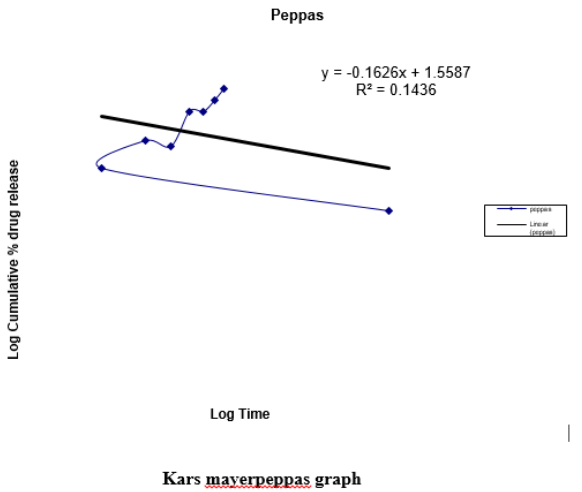
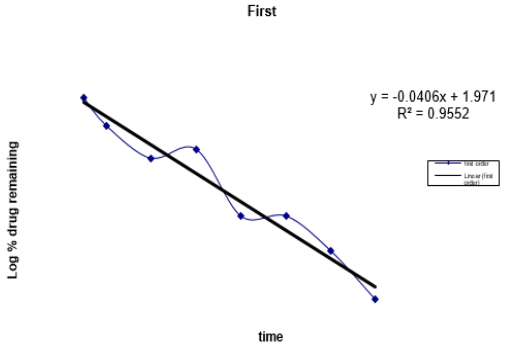


Kars mayerpeppas graph



First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed peppas mechanism.

Conclusion

- In the present research work non effervescent floating matrix formulation of Misoprostol by using various hydrophilic polymers.
- Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations.
- Non effervescent floating agent accurel concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various polymers.
- The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties.
- Among all the formulations the formulations prepared with Karaya gum retarded the drug release up to 12 hours in the concentration of 7.5 mg (F6)
- The formulations prepared by using Sodium CMC were unable to produce desired drug release, they were unable to retard drug release up to 12 hours.
- The formulations prepared with Methocel K 15M were also retarded the drug release for more than 12 hours. Hence they were not considered.
- The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

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