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FORMULATION AND IN VITRO EVALUATION OF MUCO ADHESION AND FLOATING MICROSPHERS OF ETEODOLAC USING IONIC GELATION METHOD

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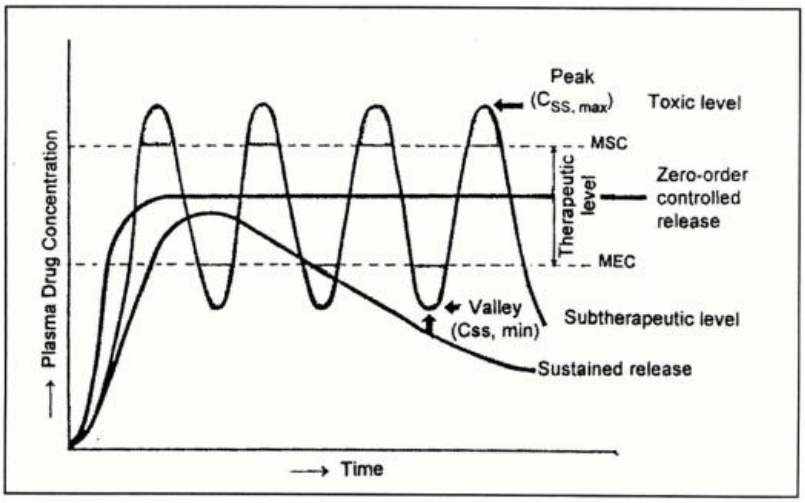
ABSTRACT

The purpose of this study is to formulation and evaluation of floating and mucoadhesion microsphere of etodolac using ionic gelatin method. The floating and mucoadhesion microspheres were studied for micromeritic properties such as Bulk density, Tapped density, Carrs index, Hausner's ratio, Angle of repose which were found to be within limits. The percentage yield of floating microsphere formulation f1 to f6 and mucoadhesive microspheres m1 to m3 were in range of 77.14±0.64 to 92.74±0.74%. The *in vitro* buoyancy of formulation f1 to f6, it was range from 71.96±1.04 to 82.96±1.07. Among all formulation f6 was found to be highest *in-vitro* buoyancy 82.96±1.07. The results also showed that the larger the particle size, the longer the floating time. The entrapment efficiency of floating microspheres f1 to f6 and mucoadhesive microspheres were in the range of 77.43±2.72 to 98.11±2.59. From the dissolution data of floating microspheres by ionic gelation method. Formulations prepared with sodium alginate alone has shown maximum drug release at 12 hr in the ratio of 1:3. Formulations prepared with sodium alginate along with Hpmc k 4m retards the drug release. Among all formulations of floating microspheres F3 was considered as optimised for floating microspheres. From the release kinetics data, it was evident that floating optimised formulation follows zero order release kinetics. From the dissolution data of mucoadhesive microspheres by ionic gelation method m1 formulation has shown maximum drug release at 12 hrs. When increase in the polymer concentration retards the drug release more than 12 hrs. Hence m1 was considered as optimised formulation for mucoadhesive microspheres. From the release kinetics data, it was evident that mucoadhesive optimised formula was followed zero order release kinetics.

KEYWORDS: Etodolac, ionic gelation method, floating and mucoadhesion microspheres.

1. INTRODUCTION

The oral route of drug administration is the most important method of administering drugs for systemic effects. The parentral route is not routinely used or not possible to self-administration of medication. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects.

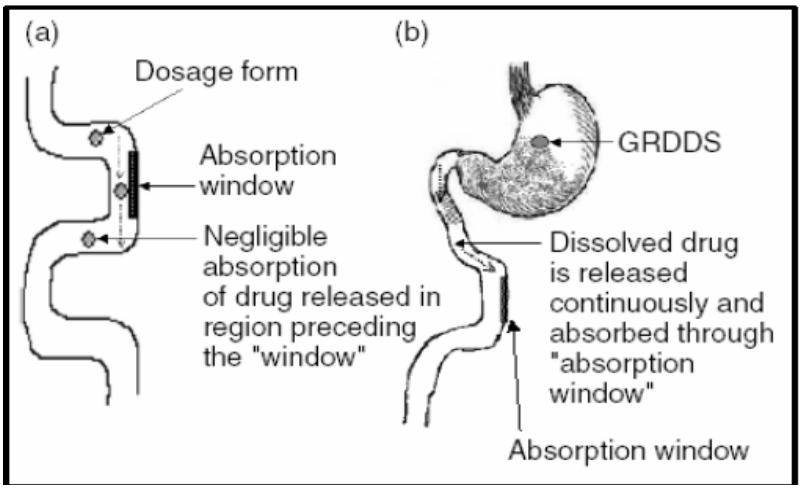


Plasma level profiles following conventional and controlled release dosing controlled release dosage forms suffer from mainly two adversities: The short gastric retention time (GRT) and unpredictable gastric emptying time (GET).[8,9] Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which resides in the stomach for a longer period of time than conventional dosage forms.[10]

Gastroretentive drug delivery system (GRDDS)

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), using gastroretentive drug delivery system (GRDDS) that will provide us with new and important therapeutic options8. Gastroretentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has

applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.



(a) Conventional drug delivery system (b) GRDDS

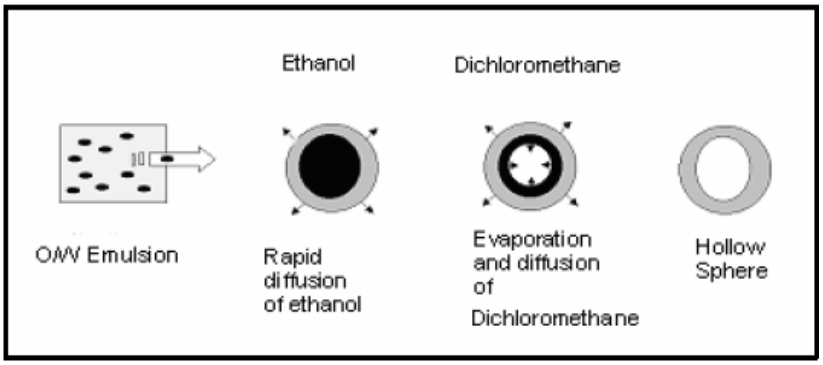
Classification of FDDS

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories *viz.* Non-effervescent and effervescent systems.

A. Non-Effervescent systems

1. Colloidal gel barrier systems:
2. Micro- porous compartment system:
3. Alginate beads.
4. Hollow Microspheres.

Hollow microspheres (microballoons) were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug (Fig1.10).



Mechanism of microballoon formation by emulsion-solvent diffusion method.

B. Effervescent systems

1. Volatile liquid containing systems
2. Gas generating systems.

2. METHODOLOGY

Material and sources

S. No	List of Chemicals	Manufacturing Company
1	Etodolac	Sura Labs
2	Sodium alginate	Merk specialiities Pvt Limited, Mumbai
3	Carbopol 934	Merk specialiities Pvt Limited, Mumbai
4	Calcium chloride	Merk specialities Pvt Limited, Mumbai
5	Hpmc k 4m	Merk specialities Pvt Limited, Mumbai
6	Sodium bicarbonate	Merk specialiities Pvt Limited, Mumbai

Formulation of floating Microspheres

Formulation code	Drug (mg)	Sodium alginate (mg)	HPMC K 4M	Sodium Bicarbonate (mg)
F1	1000	1000	-	200
F2	1000	2000	-	200
F3	1000	3000	-	200
F4	1000	750	250	200
F5	1000	1500	500	200
F6	1000	2250	750	200

Formulation of Mucoadhesive Microspheres

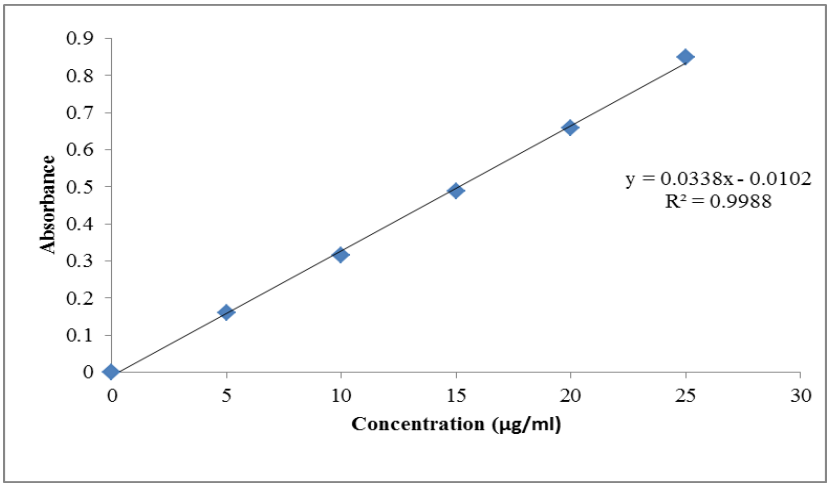
S. No	Formulation code	Drug (mg)	Sodium alginate (mg)	Carbopol 934 (mg)
1	M1	1000	500	500
2	M2	1000	1000	1000
3	M3	1000	1500	1500

3. RESULTS AND DISCUSSION

Standard calibration curve of Etodolac

Standard calibration data of Etodolac in 0.1N HCL at 225nm

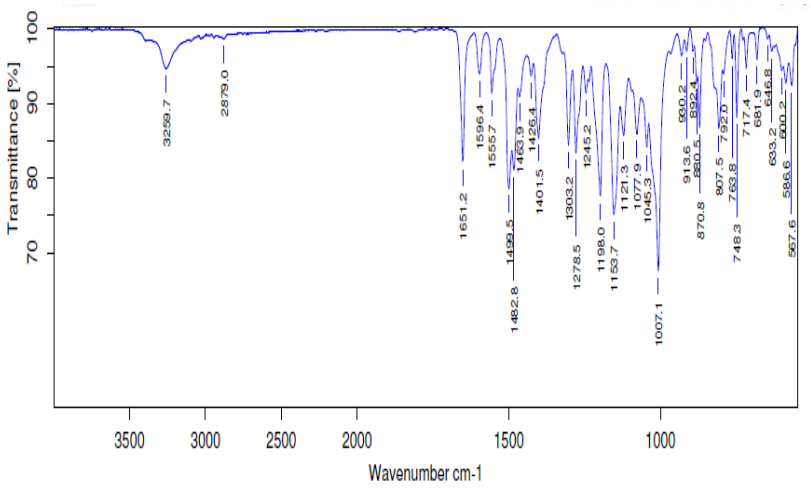
Concentration (µg/ml)	Absorbance
0	0
5	0.161
10	0.316
15	0.488
20	0.658
25	0.850



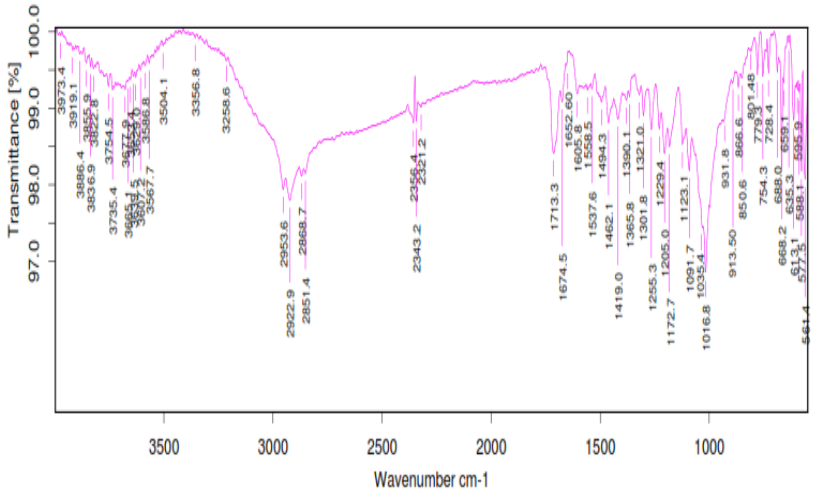
Standard calibration curve of Etodolac in 0.1N HCl

Preformulation studies

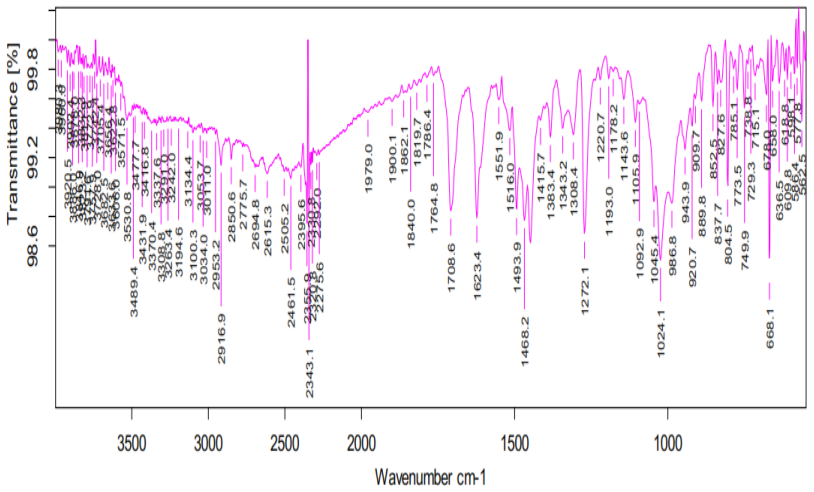
Drug- Excipient Compatability studies



FTIR of Etodolac pure drug

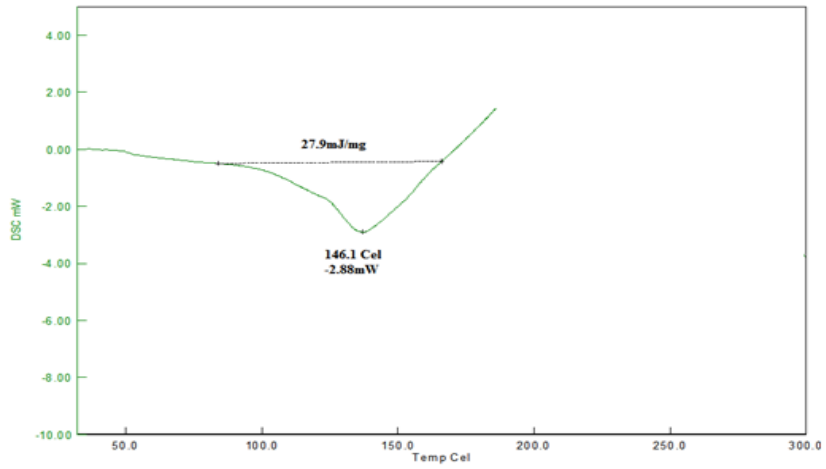


FTIR of Optimized Floating Microspheres F3 formula

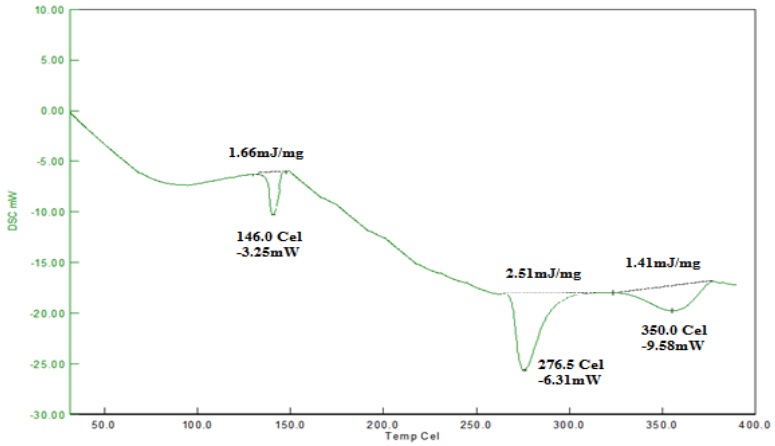


FTIR of Optimized Mucoadhesive Microspheres M1 formula

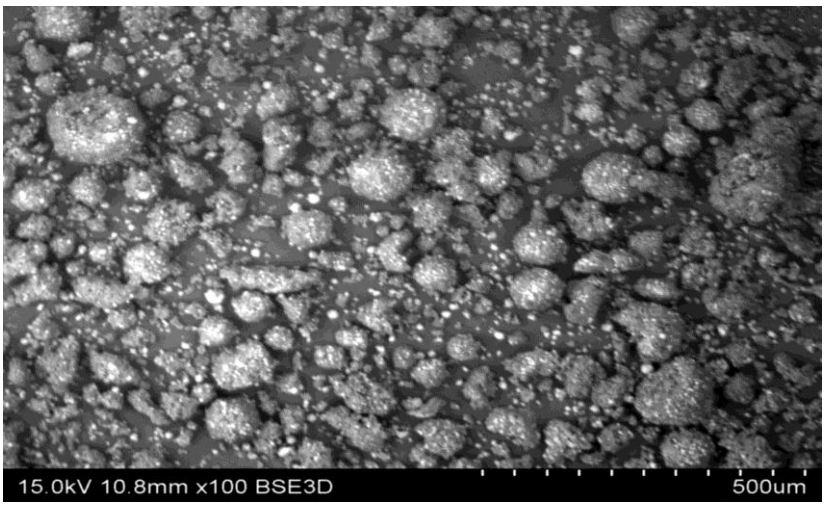
DSC Studies



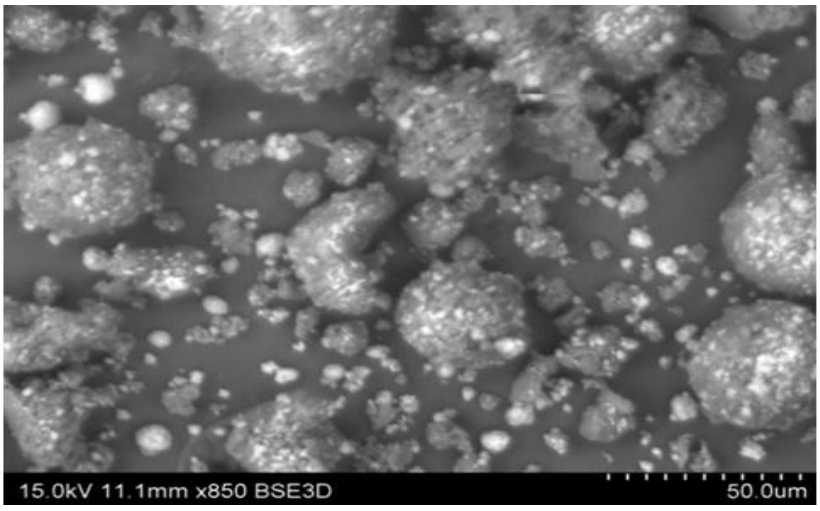
DSC of Etodolac pure drug



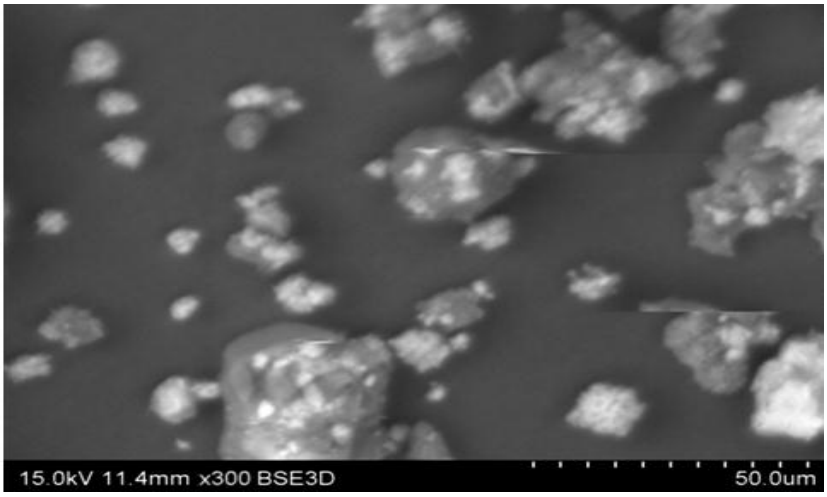
DSC of Etodolac + Sodium alginate +Hpmc k 4m.



SEM of Etodolac pure drug



SEM of Etodolac Floating Microspheres optimised F3 formulation



SEM of Etodolac Mucoadhesive Microspheres M1 optimised formulation

Evaluation of Microspheres

Micrometric Properties

S. No	Formulation code	Mean partical size (µm)	Bulk density (gm. /cm^3)	Tapped density (gm. /cm^3)	Hausners ratio	Carrr's Index	Angle of Repose(θ)
1	F1	381.55±2.54	0.32±0.010	0.39±0.018	1.21±0.04	11.13±0.11	28.49±1.71
2	F2	455.22±2.52	0.35±0.012	0.40±0.015	1.14±0.05	12.5±0.64	27.72±1.89
3	F3	471.52±2.05	0.40±0.007	0.47±0.014	1.17±0.03	14.8±0.24	30.88±2.78
4	F4	385.15±1.08	0.36±0.014	0.44±0.014	1.22±0.01	18.18±0.33	27.00±1.93
5	F5	451.84±2.07	0.41±0.015	0.47±0.015	1.14±0.02	12.76±0.26	26.02±1.80
6	F6	493.24±2.43	0.40±0.012	0.48±0.021	1.2±0.01	16.66±0.33	26.56±1.43
7	M1	473.9±2.16	0.39±0.018	0.45±0.022	1.15±0.03	13.33±1.5	26.80±1.68
8	M2	482.12±2.21	0.41±0.015	0.48±0.027	1.17±0.01	14.5±0.86	27.11±1.59
9	M3	477.5±2.15	0.44±0.017	0.50±0.015	1.13±0.02	12±0.35	26.56±1.68

All values represented as mean ± standard deviation (n=3)

Percentage yield, *in vitro* buoyancy and incorporation efficiency of floating microspheres of Etodolac

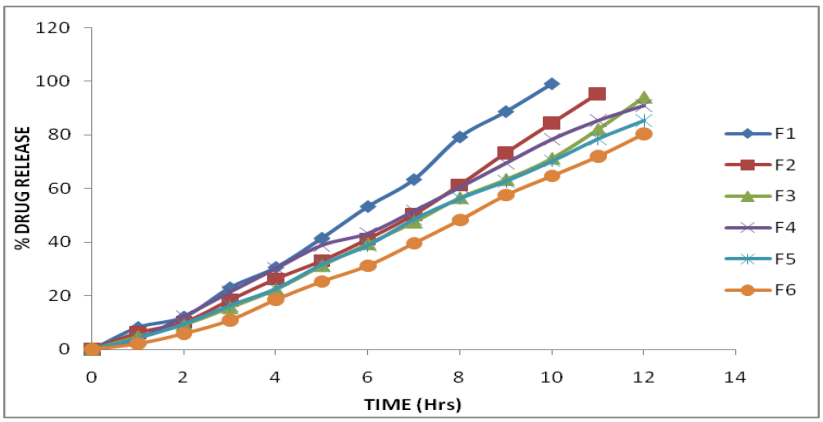
S. No	Formulation code	Percentage yield	*In vitro* buoyancy (in sec)	Entrapment Efficiency (%)
1	F1	77.14±0.64	71.96±1.04	77.43±2.72
2	F2	82.29±0.69	75.43±2.02	87.34±2.84
3	F3	85.35±0.66	79.32±0.97	87.11±3.01
4	F4	93.08±0.72	73.41±1.03	92.30±2.88
5	F5	80.48±0.65	75.33±1.32	79.76±1.58
6	F6	86.05±0.51	82.96±1.07	91.94±2.17
7	M1	90.17±0.43	-	98.11±2.59
8	M2	92.74±0.74	-	83.91±2.02
9	M3	90.64±0.55	-	90.38±2.34

All values represented as mean ± standard deviation (n=3)

In Vitro drug release

***In-Vitro* drug release data of Etodolac floating microspheres F1 to F6**

S. No	Time (Hrs)	Cumulative %drug release					
		F1	F2	F3	F4	F5	F6
	0	0	0	0	0	0	0
1	1	8.24 ± 0.98	6.22 ± 1.05	4.83 ± 1.15	4.07 ± 1.28	4.23 ± 1.11	2.16±1.24
2	2	12.14 ± 1.25	10.11 ± 1.12	9.23 ± 2.24	12.32 ± 0.98	9.56 ± 1.64	5.91±1.52
3	3	23.08 ± 2.05	18.42 ± 1.85	15.65 ± 1.08	21.44 ± 2.01	16.43 ± 1.54	10.96±1.47
4	4	30.64 ± 1.56	26.32 ± 2.04	22.42 ± 0.98	30.23 ± 1.41	22.71 ± 2.12	18.65±0.97
5	5	41.55 ± 1.81	33.08 ± 2.17	31.32 ± 1.64	38.86 ± 1.06	31.78 ± 0.95	25.41±2.17
6	6	53.34 ± 2.14	41.15 ± 1.53	39.44 ± 1.55	43.29 ± 1.75	38.92 ± 1.04	31.32±1.61
7	7	63.41 ± 1.74	50.28 ± 1.67	47.54 ± 1.34	51.65 ± 2.11	48.64 ± 2.06	39.68±2.05
8	8	79.27 ± 2.05	61.33 ± 1.74	56.63 ± 1.27	60.46 ± 1.62	56.38 ± 1.26	48.36±1.04
9	9	88.75 ± 1.34	73.28 ± 1.97	63.43 ± 1.31	69.45 ± 1.47	62.81 ± 1.40	57.65±1.67
10	10	99.12 ± 2.08	84.36 ± 2.17	71.32 ± 1.55	78.34 ± 1.09	70.30 ± 1.55	64.84±2.21
11	11		95.34 ± 2.08	82.14 ± 2.43	85.34 ± 1.14	78.64 ± 1.07	72.11±1.33
12	12			94.14 ± 2.11	90.91 ± 2.07	85.48 ± 2.17	80.55±1.41

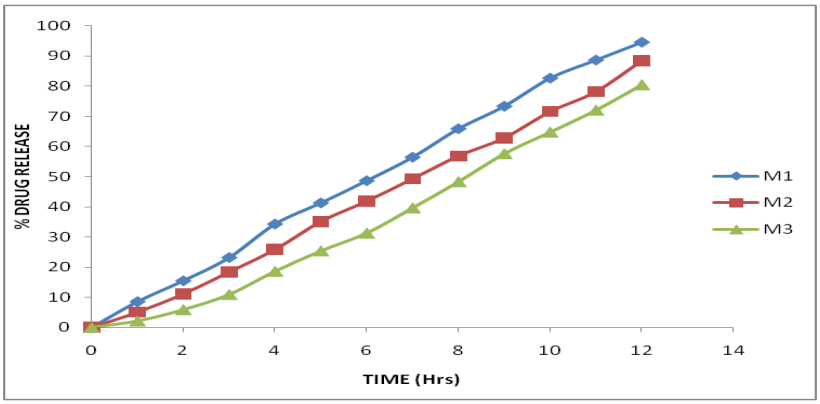


***In-Vitro* drug release profile of Etodolac Floating microspheres**

***In-Vitro* drug release data of Etodolac Mucoadhesive microspheres**

S. No	Time (hr)	Cumulative % Drug Release		
		M1	M2	M3
1	0	0	0	0
2	1	8.56 ± 1.67	5.07± 1.26	2.16±1.24
3	2	15.48 ± 2.15	11.12± 0.98	5.91±1.52
4	3	23.18 ± 1.06	18.41± 1.41	10.96±1.47
5	4	34.29 ± 0.96	25.87± 0.86	18.65±0.97
6	5	41.28 ± 2.04	35.14± 0.78	25.41±2.17
7	6	48.65 ± 1.62	41.88± 1.07	31.32±1.61
8	7	56.43 ± 1.34	49.32± 1.12	39.68±2.05

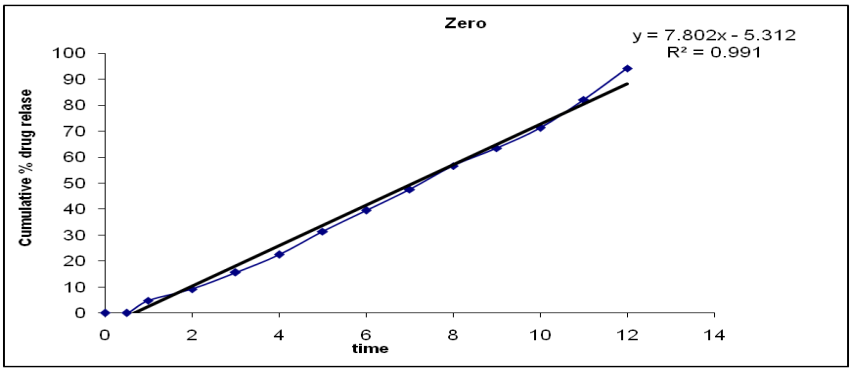
9	8	65.87 ± 2.11	56.87± 1.16	48.36±1.04
10	9	73.34 ± 1.47	62.87± 1.96	57.65±1.67
11	10	82.65 ± 1.32	71.59± 0.84	64.84±2.21
12	11	88.65 ± 2.06	78.23± 0.39	72.11±1.33
13	12	94.55±0.92	88.49± 1.64	80.55±1.41



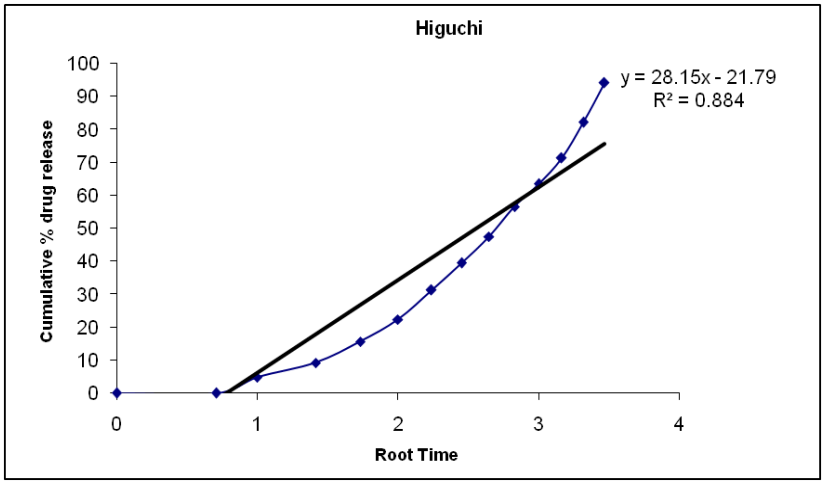
Comparison of *In-Vitro* drug release profile of Etodolac mucoadhesive microspheres

Data of Release Kinetics

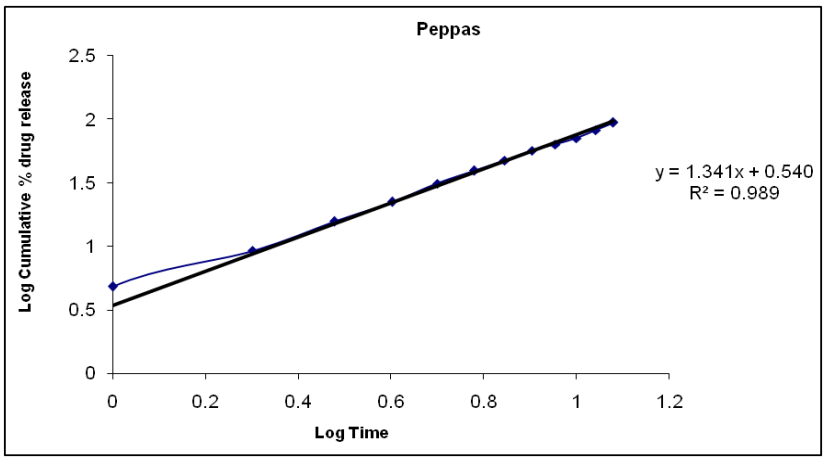
S. No	Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain
1	0	0	0			2.000
2	0	0.5	0.707	#NUM!	-0.301	2.000
3	4.83	1	1.000	0.684	0.000	1.979
4	9.23	2	1.414	0.965	0.301	1.958
5	15.65	3	1.732	1.195	0.477	1.926
6	22.42	4	2.000	1.351	0.602	1.890
7	31.32	5	2.236	1.496	0.699	1.837
8	39.44	6	2.449	1.596	0.778	1.782
9	47.54	7	2.646	1.677	0.845	1.720
10	56.63	8	2.828	1.753	0.903	1.637
11	63.43	9	3.000	1.802	0.954	1.563
12	71.32	10	3.162	1.853	1.000	1.458
13	82.14	11	3.317	1.915	1.041	1.252
14	94.14	12	3.464	1.974	1.079	0.768



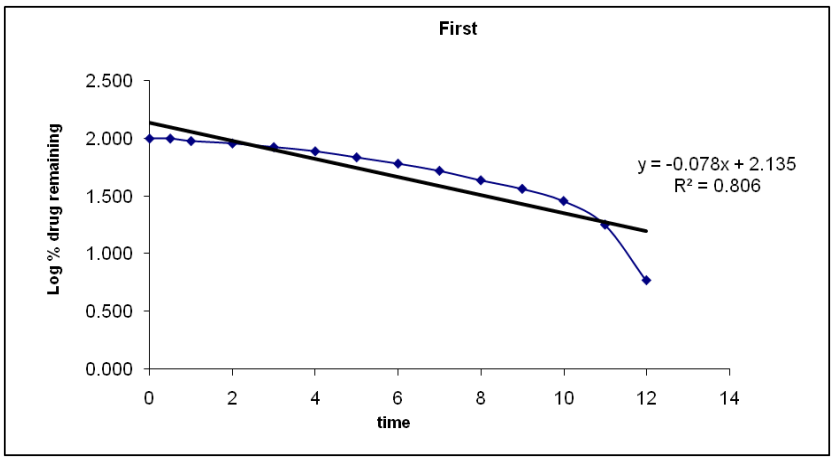
Graph of Zero order release kinetics



Graph of Higuchi release kinetics



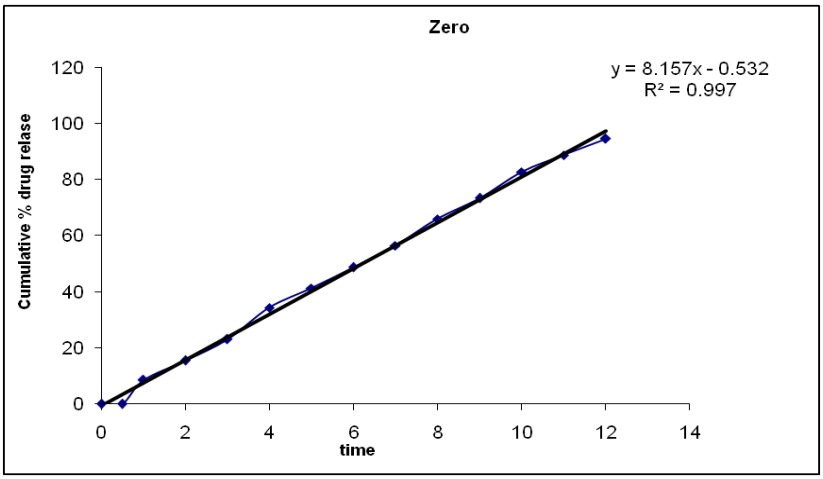
Graph of Peppas release kinetics



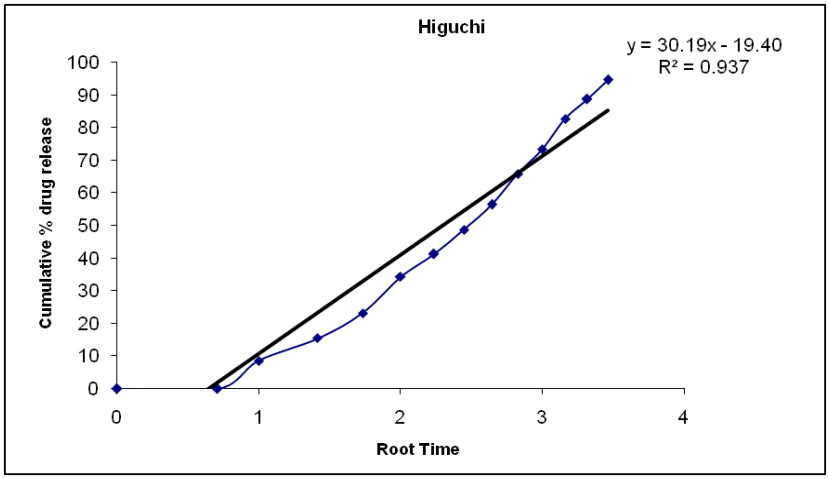
Graph of First order release kinetics

***In Vitro* Drug Release Kinetics for Mucoadhesive Microspheres M1 formulation**

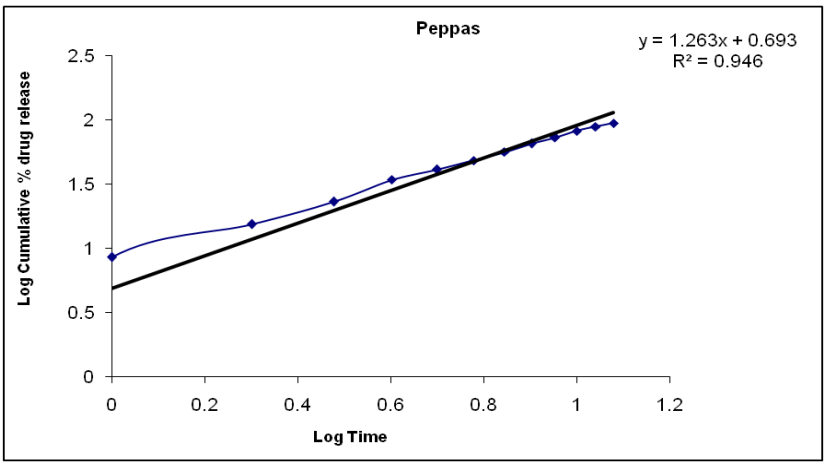
S. No	Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	LOG (%) Remain
1	0	0	0			2.000
2	8.56	1	1.000	0.932	0.000	1.961
3	15.48	2	1.414	1.190	0.301	1.927
4	23.18	3	1.732	1.365	0.477	1.885
5	34.29	4	2.000	1.535	0.602	1.818
6	41.28	5	2.236	1.616	0.699	1.769
7	48.65	6	2.449	1.687	0.778	1.711
8	56.43	7	2.646	1.752	0.845	1.639
9	65.87	8	2.828	1.819	0.903	1.533
10	73.34	9	3.000	1.865	0.954	1.426
11	82.65	10	3.162	1.917	1.000	1.239
12	88.65	11	3.317	1.948	1.041	1.055



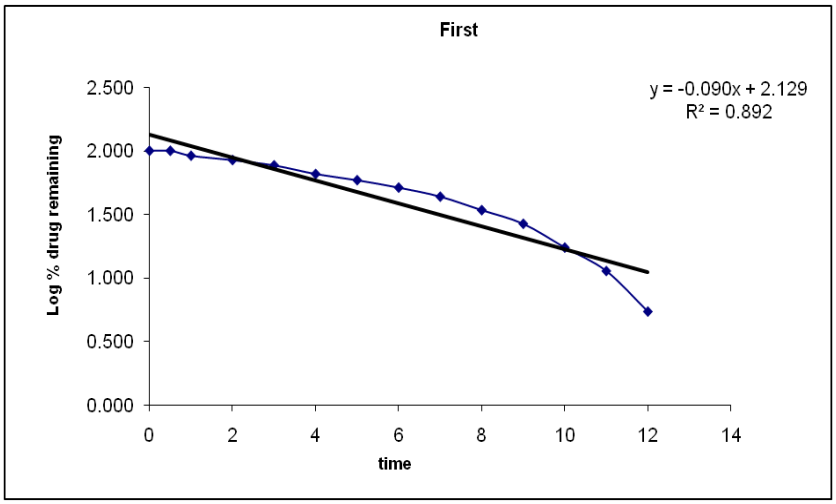
Graph of Zero order release kinetics



Graph of Higuchi release kinetics



Graph of Peppas release kinetics



Graph of First order release kinetics

From the release kinetics data, It was evident that mucoadhesive optimised formula was followed Zero order release kinetics.

CONCLUSION

The floating and mucoadhesion microspheres were studied for micromeritic properties such as bulk density, tapped density, carrs index, hausners ratio, angle of repose which were found to be within limits. The percentage yield of floating microsphere formulation f1 to f6 and mucoadhesive microspheres m1 to m3 were in range of 77.14±0.64 to 92.74±0.74%. The *in vitro* buoyancy of formulation f1 to f6, it was range from 71.96±1.04 to 82.96±1.07. Among all formulation f6 was found to be highest *in-vitro* buoyancy 82.96±1.07. The results also showed that the larger the particle size, the longer the floating time. The entrapment efficiency of floating microspheres f1 to f6 and mucoadhesive microspheres were in the range of 77.43±2.72 to 98.11±2.59.Formulations prepared with sodium alginate alone has

shown maximum drug release at 12 hr in the ratio of 1:3. Formulations prepared with sodium alginate along with Hpmc k 4m retards the drug release. Among all formulations of floating microspheres f3 was considered as optimised for floating microspheres. From the release kinetics data, it was evident that floating optimised formulation follows zero order release kinetics. From the dissolution data of mucoadhesive microspheres by ionic gelation method m1 formulation has shown maximum drug release at 12 hrs. When increase in the polymer concentration retards the drug release more than 12 hrs. Hence m1 was considered as optimised formulation for mucoadhesive microspheres. From the release kinetics data, it was evident that mucoadhesive optimised formula was followed zero order release kinetics.

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