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Design and characterization of pioglitazone hydrochloride mucoadhesive microspheres

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ABSTRACT

A Mucoadhesive microsphere of pioglitazone was prepared by orifice ionic gelation method. In this method drug and polymer are added to aqueous solution of sodium alginate. Then sodium alginate solution is added drop wise into sufficient quantity of calcium chloride solution. The standard plot of pioglitazone hydrochloride was prepared in solvent. The standard graph showed good linearity with R^2 value 0.9964. Dried mucoadhesive microspheres with different % of mucoadhesive agent with 3% and 4% sodium alginate are evaluated for characterization like swelling index, particle size analysis, *In vitro* wash off test. The formulation KF8 was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months.

Keywords: Mucoadhesive microspheres, Pioglitazone, Ionic gelation method.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly. Maintain the desired drug concentration that is the drug delivery system should deliver drug detected by the needs of the body over an entire period of treatment. This is possible through administration of conventional dosage form in a particular dose and particular frequency to provide a prompt release of drug. Therefore to achieve and maintain the concentration within the therapeutically effective range needs repeated administration in a day. This results in a significant fluctuation in a plasma drug level, leads to several undesirable toxic effects, and poor patient compliance.

Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They are designed to control the drug release from the dosage form to improve bioavailability, reduce the adverse action and prolong the action of drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during

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prolonged treatment. It is needed to formulate in long acting dosage from reaching to effective biological site rapidly. [1]

Microspheres

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm .they are made of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin**:** the synthetic polymers include polylactic acid polyglycolic acid. Microspheres are small and have large surface to volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microsphere are extremely important, often dictating their activity. [20]

METHOD

Preformulation Studies

Before formulation of drug substance into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

FORMULATION DEVELOPMENT

Preparation of mucoadhesive microspheres of pioglitazone hydrochloride

Method

Orifice ionic gelation method

Mucoadhesive microspheres of pioglitazone were prepared by orifice ionic gelation method. In this method drug and polymer are added to aqueous solution of sodium alginate. Then sodium alginate solution was added drop wise into sufficient quantity of calcium chloride solution through a syringe with a needle of size No. 18. The added droplets are retained in the calcium chloride solution for 15 to 20 min. To complete the curing reaction and to produce spherical rigid microspheres. The microspheres are collected by decantation and the product thus separated is washed repeatedly with water and dried at 45 ^{o}C for 24 h.

RESULTS AND DISCUSSION

Preformulation studies

Evaluations for optimized products

Dried mucoadhesive microspheres with different % of mucoadhesive agent with 3% and 4% sodium alginate are evaluated for characterization like swelling index, particle size analysis, *in vitro* wash off test.

Table 4.23: Swelling index

	% of M.A	Xanthan gum	Gum kondagogu	Guar gum	Gum olibanum
3% S.A	5%	400%	225%	250%	280%
	10%	430%	245%	290%	330%
	15%	470%	285%	350%	405%
	20%	520%	330%	430%	495%
4% S.A	5%	290%	170%	190%	210%
	10%	370%	215%	270%	235%
	15%	400%	250%	320%	280%
	20%	450%	290%	440%	360%

Table 4.24: Average particle size by sieve analysis method

	% of M.A	Xanthan gum	Gum kondagogu	Guar gum	Gum olibanum
3% S.A	5%	343.03µm	1060 µm	1060 µm	472.1 µm
	10%	357.5 µm	1060 µm	543.4 µm	196.56 µm
	15%	146.93 µm	548 µm	418.6 µm	543.4 µm
	20%	455.8 µm	389.53 µm	427.96 µm	554 µm
	5%	514.9 µm	401.83 µm	1060 µm	421.86 µm

4% S.A	10%	310.72 µm	578.9 µm	539.6 µm	413.33 µm
	15%	336.95 µm	398.73 µm	568.4 µm	443.13 µm
	20%	414.1 µm	437.46 µm	425.23 µm	391.03 µm

Table 4.25: Mucoadhesion Time: (Time taken to separate 60% of microspheres from mucus layer)

	% of M.A	Xanthan gum	Gum kondagogu	Guar gum	Gum olibanum
	5%	1h:30min	2h **:** 15min	3h	1h: 30min
3% S.A	10%	1h **:** 50 min	2h **:** 45min	3h:30min	2h:15 min
	15%	2h **:** 10min	3h : 30min	4h : 20min	2h: 50min
	20%	3h	4h : 35min	4h : 40min	3h:30min
	5%	3h	4h:20min	5h:30min	3h:40min
4% S.A	10%	3h:30min	4h:45min	6h:10min	4h:35min
	15%	3:45min	5h:30min	6h: 30min	4h:45min
	20%	4h	7hrs	7hrs	6h:30min

Formulation data according to experimental designs

Table 4.27: Formulation chart for formulations with xanthan gum

S.no	Ingredient	XF1	XF2	XF3	XF4	XF5	XF6	XF7	XF8	XF9
1	**S.A (%)**	3.5	4	3.5	3	3	4	3	3.5	4
2	**XG(%)**	17.5	20	20	17.5	15	15	20	15	17.5

Table 4.28: Formulation chart for formulation with guar gum

S.no	Ingredient	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9
1	**S.A (%)**	3	3.5	4	3.5	3.5	3	4	3	4
2	**GG(%)**	10	5	5	7.5	10	5	10	7.5	7.5

Table 4.29: Formulation chart for formulation with gum kondagogu:

S.no	Ingredient	KF1	KF2	KF3	KF4	KF5	KF6	KF7	KF8	KF9
1	**S.A (%)**	3.5	3.5	4	4	3	4	3	3.5	3
2	**GK (%)**	12.5	15	15	10	15	12.5	10	10	12.5

Table 4.30: Formulation chart for formulation with gum olibanum:

S.no	Ingredient	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
1	**S.A (%)**	3	3.5	4	3.5	4	3	3	3.5	4
2	**GO (%)**	5	10	10	7.5	5	10	7.5	5	7.5

EVALUATIONS FOR MUCOADHESIVE MICROSPHERES

Dried mucoadhesive microspheres are evaluated for characteristics like flow properties, production yield, particle size analysis, swelling index, *in vitro* wash off test & *in vitro* drug release studies.

Flow properties of microspheres

The results of the physical tests of many of the blends were in the limits and comply with the standards. The tests performed are bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose.

Table 4.35: Characterization of microspheres with Xanthan gum

Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose(degrees)

XF1	0.416	0.452	8	1.08	10.08
XF2	0.455	0.5	10	1.1	8.47
XF3	0.35	0.4	14.5	1.14	15.01
XF4	0.45	0.51	12.08	1.13	17.19
XF5	0.50	0.56	12.27	1.12	12
XF6	0.47	0.5	6	1.06	11.9
XF7	0.53	0.59	10.92	1.11	17.5
XF8	0.33	0.37	12.74	1.12	23.6
XF9	0.28	0.36	22.2	1.28	12.9

Table 4.36: Evaluation report of mucoadhesive microspheres with Xanthan gum

Formulations	Percentage yield (%)	Swelling index (%)	Avg particle size (µm)	Mucoadhesion time	Assay (%)
XF1	76.63	470	326.52	2h: 45 min	95
XF2	65	510	271.25	3h **:** 30 min	94.3
XF3	73.9	500	273.28	2h **:** 50min	94
XF4	64.5	465	294	3h	95.6
XF5	68.42	370	309.4	4h	96
XF6	63.9	380	356.5	4h	97.8
XF7	77.5	490	390.9	3h	98
XF8	99	375	379.6	3h:45min	95.7
XF9	93.3	460	415.3	3h:30min	94.6

Table 4.37: Characterization of microspheres with Guar Gum

	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose(degrees)
GF1	0.34	0.36	7.98	1.05	17.24
GF2	0.23	0.25	8.08	1.08	15.0
GF3	0.33	0.35	5.71	1.06	12.8
GF4	0.24	0.27	11.5	1.12	17.9
GF5	0.26	0.27	7.06	1.03	12.5
GF6	0.4	0.43	7.15	1.07	11.8
GF7	0.56	0.6	6.66	1.07	17.9
GF8	0.34	0.36	6.5	1.05	10.71
GF9	0.46	0.50	8.83	1.08	18.92

Table 4.38: Evaluation report of mucoadhesive microspheres with Guar gum

Formulation	Percentage yield (%)	Swelling index (%)	Avg particle size (µm)	Mucoadhesion time	Assay (%)
GF1	91.47	345	473.6	3h : 45min	96
GF2	90.44	300	371.1	3h:30min	95.3
GF3	95.9	340	460.8	4hrs	94

GF4	96.8	370	733	4hrs	95.6
GF5	93	355	525.8	4h : 30min	96
GF6	90.3	275	388.6	4h:30min	97.8
GF7	79	330	352.3	5hrs	97
GF8	95.2	330	455.9	4hrs	95.7
GF9	96.03	385	145.4	4h:30min	95.6

Table 4.39: Characterization of microspheres with Gum Kondagogu

	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose(degrees)
KF1	O.45	0.49	8.63	1.08	24.1
KF2	0.48	0.52	7.69	1.08	12.6
KF3	0.51	0.53	5.18	1.03	15.3
KF4	0.49	0.51	3.92	1.04	11.59
KF5	0.44	0.48	8.64	1.09	15.12
KF6	0.40	0.41	4.06	1.02	25.1
KF7	0.34	0.37	10.48	1.08	12.95
KF8	0.31	0.34	10.94	1.09	20.5
KF9	0.28	0.31	12.09	1.10	13.3

Table 4.40: Evaluation report of mucoadhesive microspheres with Guar Kondagogu

Formulation	Percentage yield (%)	Swelling index (%)	Avg particle size (µm)	Mucoadhesion time	Assay (%)
KF1	97.7	270	400.3	3hrs **:** 45min	95
KF2	97.7	245	591	4h **:** 30min	94.7
KF3	96.9	295	587.6	4hrs	95.4
KF4	96.12	315	613.1	4hrs	96
KF5	97.74	200	388.8	3h : 30min	98
KF6	95.4	325	584.5	3h:45min	97.8
KF7	96.8	285	342.2	4hrs	96.4
KF8	96.8	255	429.2	4:30min	95.7
KF9	96.9	235	381.8	5hrs	98

Table 4.41: Characterization of microspheres with Gum Olibanum

	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose(degrees)
OF1	0.34	0.37	8.61	1.08	12.2
OF2	0.34	0.36	7.40	1.05	17.96
OF3	0.35	0.37	7.7	1.05	16.5
OF4	0.30	0.34	12.2	1.1	18.9

OF5	0.4	0.42	6.80	1.05	10.5
OF6	0.32	0.36	13.2	1.12	12.6
OF7	0.29	0.31	7.36	1.06	12.9
OF8	0.33	0.36	10.76	1.09	16.31
OF9	0.42	0.48	12.5	1.14	16.82

Table 4.42: Evaluation report of mucoadhesive microspheres with Gum Olibanum

Formulation	Percentage yield (%)	Swelling index (%)	Avg particle size (µm)	Mucoadhesion time	Assay (%)
OF1	95.9	320	428.8	4h : 45min	95
OF2	93.7	310	426.7	5h: 30 min	95.7
OF3	96.8	365	431.8	4h : 30min	96.4
OF4	97.6	345	402.3	5hrs	97
OF5	96.7	365	344.7	6hrs	97.4
OF6	96.8	300	594.4	6hrs	96.8
OF7	96.8	335	460.9	5hrs	95.4
OF8	95.1	360	570.1	5h:45min	96.7
OF9	95.2	290	438.6	5h:30min	97

IN VITRO DRUG RELEASE DATA AND PROFILE

Table No. 4.43: Drug release profiles of formulations containing Xanthane Gum

Time (hrs)	XF1	XF2	XF3	XF4	XF5	XF6	XF7	XF8	XF9
0	0	0	0	0	0	0	0	0	0
0.25	12.87968	14.27092	16.69841	15.15657	15.62988	15.62988	14.25299	14.90558	12.85458
0.5	21.09068	24.71275	26.50114	26.39576	23.96731	23.61233	24.69472	23.22106	21.07978
0.75	23.64211	32.33645	34.83749	32.72719	28.8438	28.46892	31.97052	27.65598	34.65347
1	24.78357	34.05315	35.07273	35.15594	33.58171	32.86412	34.0294	32.42319	35.75928
1.5	26.41829	35.47002	36.98271	35.99438	35.66657	35.80199	35.96966	34.7491	36.03831
2	27.6131	50.61604	43.42375	53.79657	42.85363	43.8504	54.20213	41.39333	41.43452
3	28.41273	52.78895	47.21379	54.7396	44.17674	45.29183	56.40731	42.59091	42.31301

4	29.67215	52.99823	48.97748	56.4336	44.955	45.9596	56.81398	43.35414	43.54418
5	30.36125	54.00104	49.76837	57.19771	45.62998	46.78164	57.58141	44.08212	44.30886
6	30.77086	54.15596	50.16907	60.19976	46.17598	47.17789	57.82593	44.64557	44.56856
7	34.02966	55.20447	51.24949	60.33552	46.34485	47.24638	58.83904	44.79254	48.21089
8	36.30966	56.95431	51.99865	60.7802	46.79423	47.86016	60.2234	45.28804	50.36022
9	39.14357	57.49102	53.22863	61.92277	48.146	49.26968	60.98066	46.6073	52.84757
10	41.08578	58.08789	54.82375	61.96135	48.51552	49.7654	61.73476	47.01585	55.42018
11	42.21373	58.32931	57.43142	63.09067	49.18455	50.58283	62.01595	47.69543	56.10275
12	42.83478	58.50012	58.93809	64.80114	50.17265	51.20741	62.53514	48.69774	56.9357

Comparative dissolution profile of XF1 to XF3 Formulations with Xanthan gum

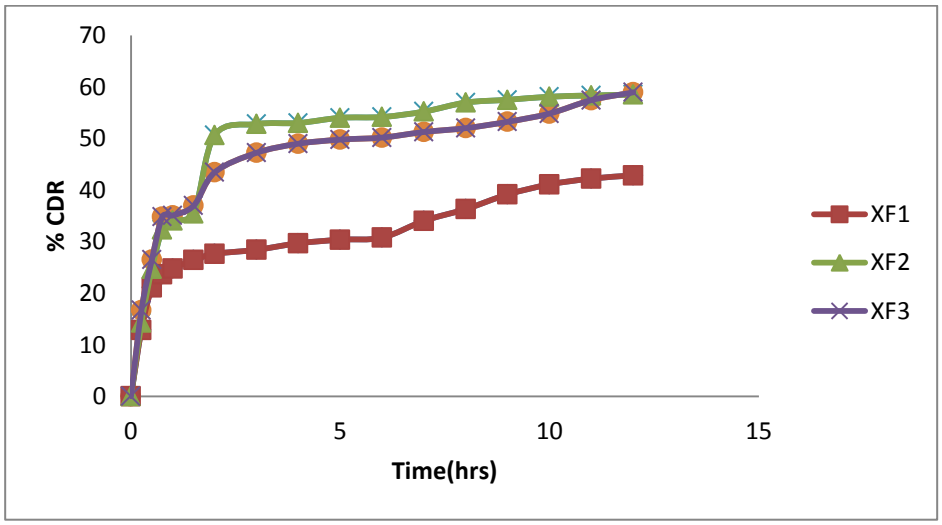

Figure 25: *In Vitro* drug release of pioglitazone (XF1 to XF3)

Comparative dissolution profile of XF4 to XF6 Formulations with Xanthan gum

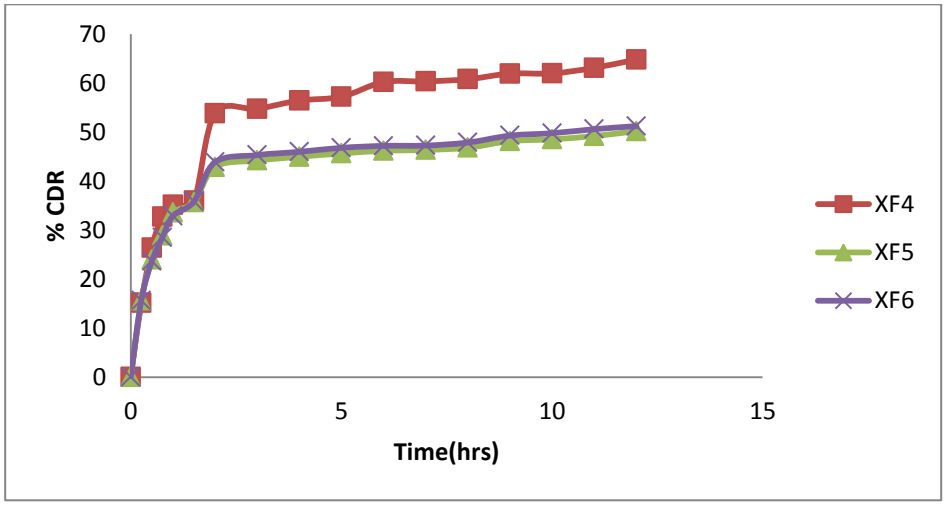

Figure 26: *in vitro* drug release of pioglitazone (XF4 to XF6)

Comparative dissolution profile of XF7 to XF9 Formulations with Xanthan gum

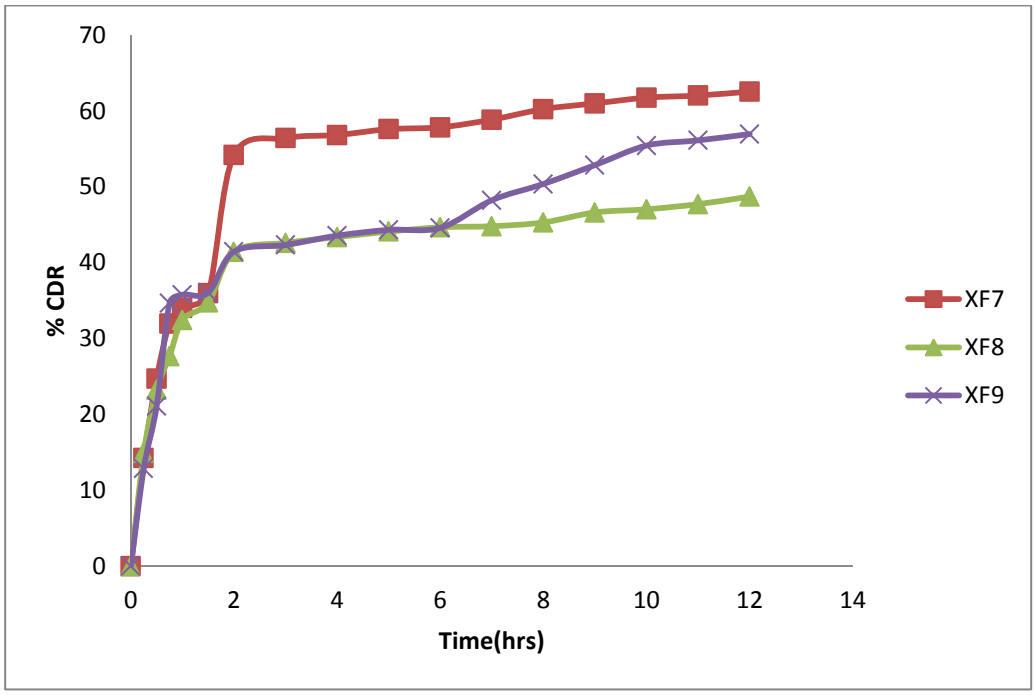

Figure 27: *in vitro* drug release of pioglitazone (XF7 to XF9)

Table No. 4.44: Drug release profiles of formulations containing Guar Gum

Time (hrs)	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9
0	0	0	0	0	0	0	0	0	0
0.25	8.422709	6.687251	8.72749	5.790837	5.568526	7.565737	9.591633	9.978884	9.204382
0.5	13.60775	11.86584	9.564821	10.48436	7.761614	13.88984	14.78675	17.70046	10.2846
0.75	18.34444	15.72034	11.62566	14.38625	10.78424	16.84606	21.36582	21.46303	10.91875
1	20.86241	18.60392	13.1849	16.77843	12.96287	19.69277	21.65946	22.33799	15.05928
1.5	25.31213	23.79428	15.48034	21.05875	15.41861	25.48068	27.33974	27.58448	17.8958
2	27.41223	26.23044	20.5957	22.87388	18.79476	29.58978	30.69514	33.28972	20.29223
3	29.40426	28.65076	22.6216	23.27547	21.52345	30.79098	37.1063	38.89052	22.70896
4	32.75157	30.34229	25.11413	27.0534	24.10235	31.89486	37.33554	39.95072	24.16382
5	32.95329	30.76666	25.85271	27.48179	28.63175	32.66062	37.71287	40.85528	27.37291

6	33.13444	31.55181	26.27972	28.17776	32.34711	33.67797	37.93074	41.12283	29.56345
7	33.35588	32.64956	26.98146	29.16432	32.99556	34.89809	38.16394	42.12311	31.77311
8	33.96203	33.48074	27.50046	30.07372	33.85157	35.17107	38.38747	43.41197	34.33898
9	34.23791	34.08685	28.44885	30.44655	34.42147	36.02988	38.65863	44.10534	36.05104
10	34.97408	34.63875	29.725	31.30888	35.81878	37.38811	38.90237	44.50823	36.87217
11	36.77908	35.29028	30.84307	32.39091	37.66801	38.89711	39.2297	44.98115	39.18544
12	37.62576	36.20693	32.18939	33.87312	39.9501	40.52542	39.48689	45.71096	40.83695

Comparative dissolution profile of GF1 to GF3 Formulations with Guar gum

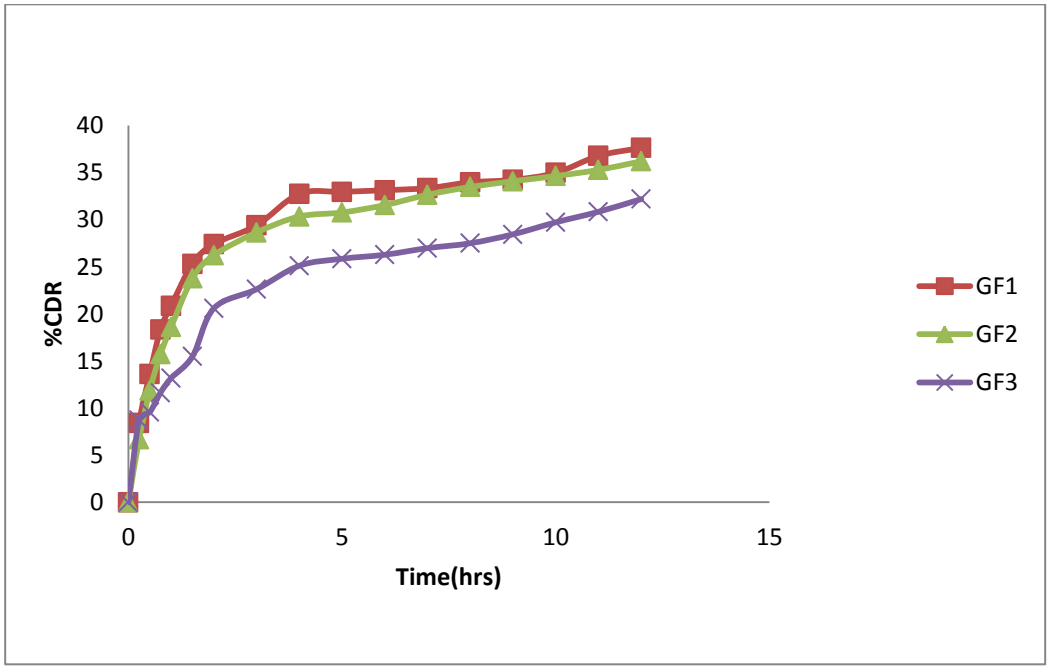

Figure 28: *in vitro* drug release of pioglitazone (GF1 to GF3)

Comparative dissolution profile of GF4 to GF6 Formulations with Guar gum

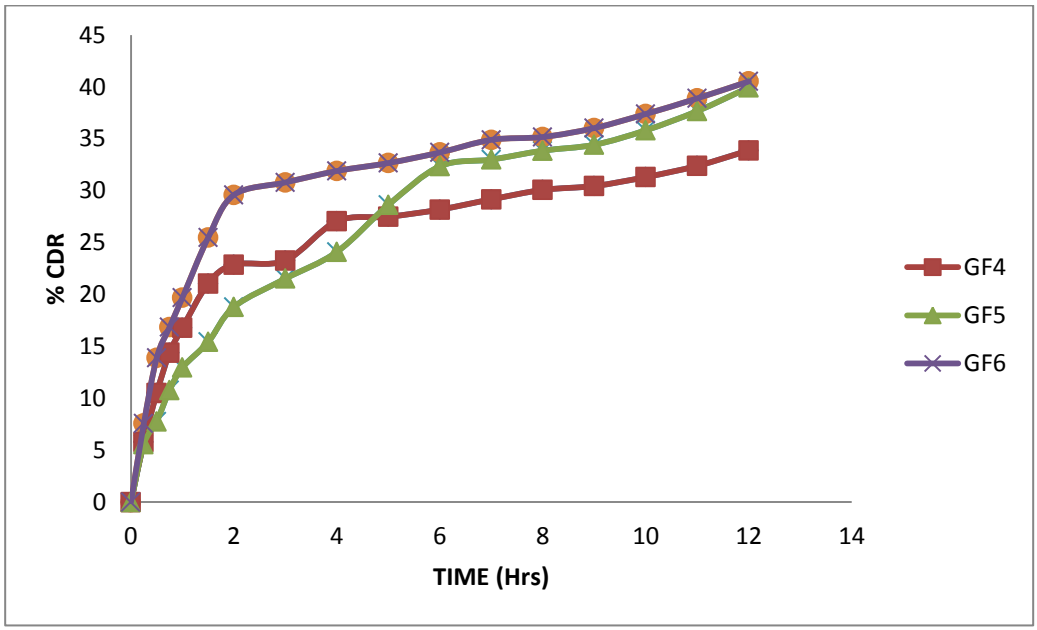

Figure 29: *in vitro* drug release of pioglitazone (GF4 to GF6)

Comparative dissolution profile of GF7 to GF9 Formulations with Guar gum

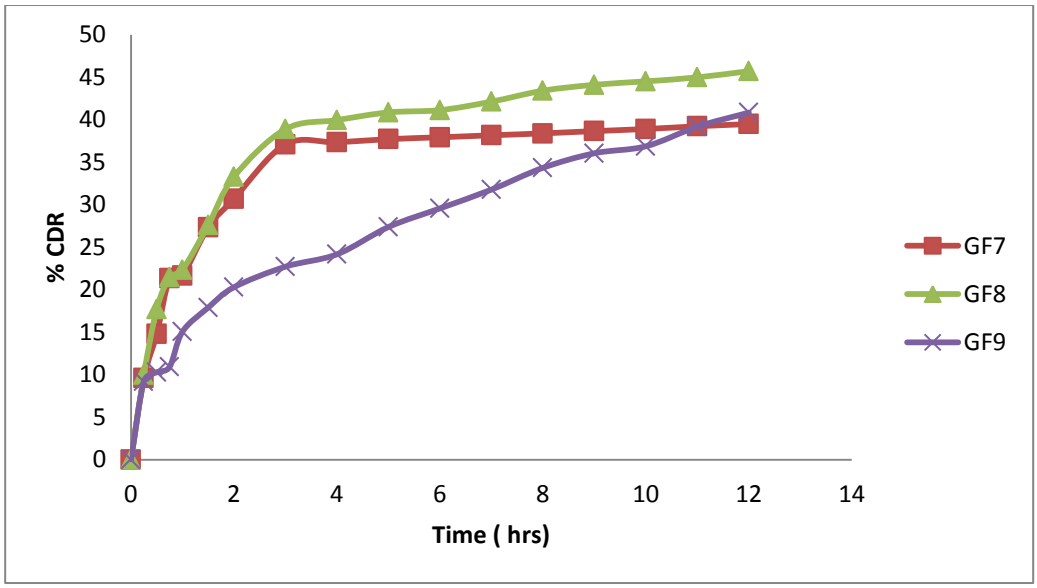

Figure 30: *in vitro* drug release of pioglitazone (GF7 to GF9)

Table No. 4.45: Drug release profiles of formulations containing Gum Kondagogu

Time (hrs)	KF1	KF2	KF3	KF4	KF5	KF6	KF7	KF8	KF9
0	0	0	0	0	0	0	0	0	0
0.25	8.566135	11.27689	11.21594	11.5243	11.62112	11.26972	11.99402	12.27371	11.19801

0.5	10.84759	13.1754	13.2898	13.57478	13.56456	13.1646	14.36265	14.48612	12.78771
0.75	12.93707	15.03749	15.98799	15.63271	16.02761	15.62902	16.39267	16.83235	16.09984
1	15.1454	17.5908	18.67207	17.5905	19.02026	19.0139	18.2399	18.99755	19.41922
1.5	17.90703	19.89608	21.27735	20.54833	21.72785	21.72149	21.3949	21.6153	22.36213
2	21.27876	22.82677	24.25869	22.09496	24.66863	24.379	24.58839	24.96056	24.68255
3	24.30147	25.49092	27.27781	24.43998	27.68775	27.12203	27.56807	28.11235	28.22159
4	26.15054	28.78659	30.60414	28.79524	31.81727	31.13169	31.71888	32.26054	31.82691
5	28.97432	31.35468	33.78034	31.66147	34.63936	34.03406	33.8345	34.46315	34.2653
6	31.97859	33.55319	35.55406	33.7259	37.4805	36.86988	36.67878	37.46303	37.57398
7	34.61205	36.09353	37.98635	36.56524	39.67735	39.02195	39.19078	40.15299	39.6888
8	37.10922	39.30024	40.35293	38.95745	42.82187	42.04616	41.80958	42.55631	42.36
9	39.41189	41.59926	43.66809	41.1904	45.26269	44.69946	44.4138	45.35261	45.27865
10	41.55835	44.15797	46.26253	43.61811	47.83125	48.26339	46.32201	47.13841	48.97671
11	43.79147	46.49367	49.03932	46.18064	50.30231	49.54809	49.69958	50.49327	50.32817
12	46.42365	48.39349	50.81255	48.35875	52.1338	51.00056	51.56418	52.4139	51.40671

Comparative dissolution profile of KF1 to KF3 Formulations with Gum Kondagogu

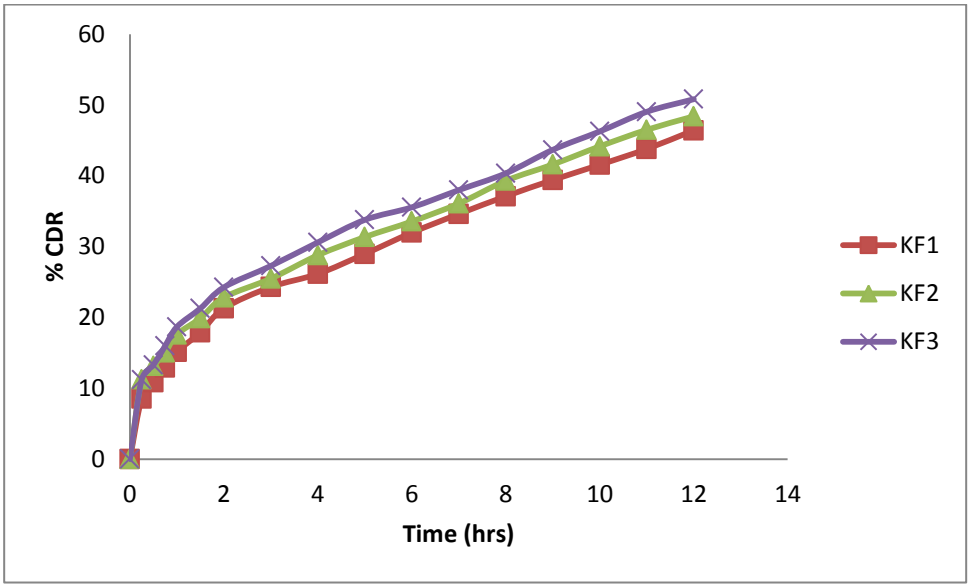

Figure 31: *in vitro* drug release of pioglitazone (KF1 to KF3)

Comparative dissolution profile of KF4 to KF6 Formulations with Gum Kondagogu

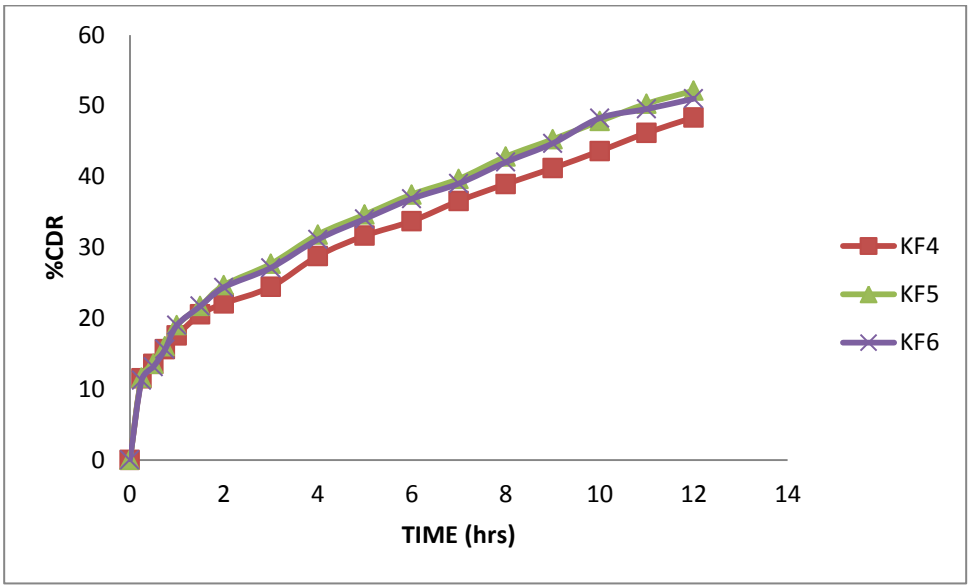

Figure 32 : *in vitro* drug release of pioglitazone (KF4 to KF6)

Comparative dissolution profile of KF7 to KF9 Formulations with Gum Kondagogu

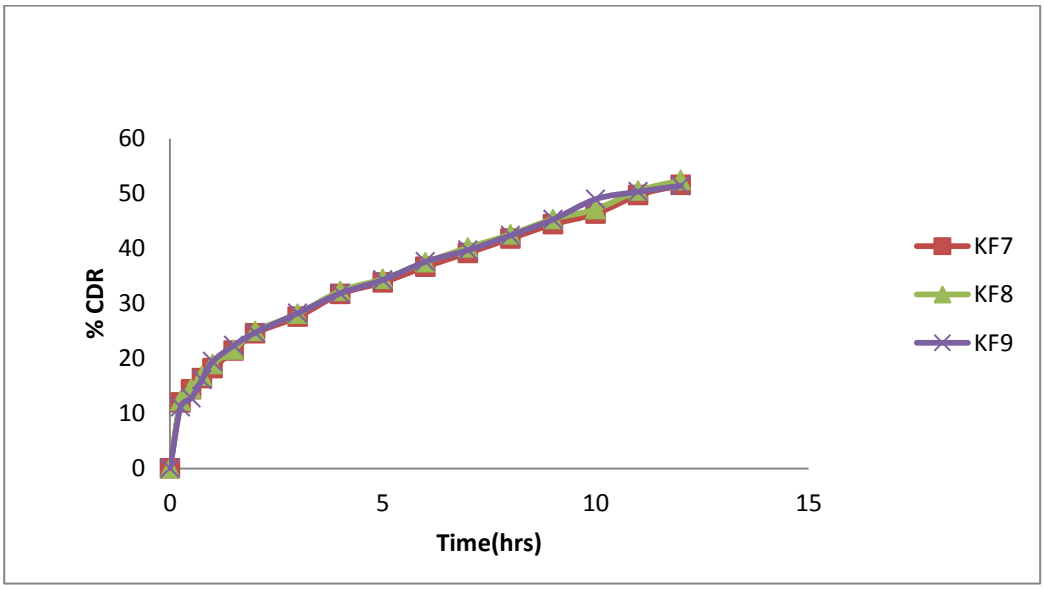

Figure 33 : *in vitro* drug release of pioglitazone (KF7 to KF9)

Table No. 4.46: Drug release profiles of formulations containing Gum Olibanum

Time (hrs)	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
0	0	0	0	0	0	0	0	0	0
0.25	14.2745	11.5243	11.6749	13.77251	13.71873	13.58606	14.81594	13.38167	14.81594
0.5	16.44066	13.57478	14.36805	15.96456	16.04315	15.5691	16.45801	15.67912	16.45801
0.75	18.03036	15.63271	16.82839	17.48709	17.55894	16.21813	18.15177	17.23235	18.15177

1	20.4997	17.5905	18.78203	20.09687	20.12968	20.61012	20.95165	19.85867	21.14528
1.5	22.6595	20.54833	21.78586	21.99631	22.06875	22.35829	23.16056	21.83928	23.16163
2	25.06375	22.09496	24.03129	24.66227	25.05064	25.63586	25.94046	25.51556	25.94153
3	28.60996	24.43998	27.11855	27.74952	28.59685	28.78406	29.48667	28.65659	28.92122
4	31.01412	28.79524	32.04805	31.39536	31.8042	33.19398	33.69084	33.05572	33.68876
5	34.23472	31.66147	34.92516	33.43347	34.62408	35.67412	35.12143	35.4748	35.11936
6	36.35789	33.7259	36.84988	35.59743	36.82835	38.12837	38.82229	38.32661	38.82022
7	38.72922	36.56524	39.0001	37.52215	39.52863	40.23737	41.05896	40.36926	41.229
8	41.98112	38.95745	41.37701	40.78751	42.39773	42.82743	44.09651	43.64199	43.52886
9	43.43631	41.1904	44.34038	42.475	43.77635	44.78602	45.8704	46.07189	45.86614
10	45.84211	43.61811	46.13641	44.91361	46.18044	46.3462	47.7253	47.04821	47.72104
11	47.98821	46.18064	48.76651	47.03534	48.36783	48.2049	49.9162	49.24127	49.91193
12	50.76592	48.35875	50.01215	49.51964	50.91813	50.68287	51.83892	51.23432	51.4761

Comparative dissolution profile of OF1 to OF3 Formulations with Gum Olibanum

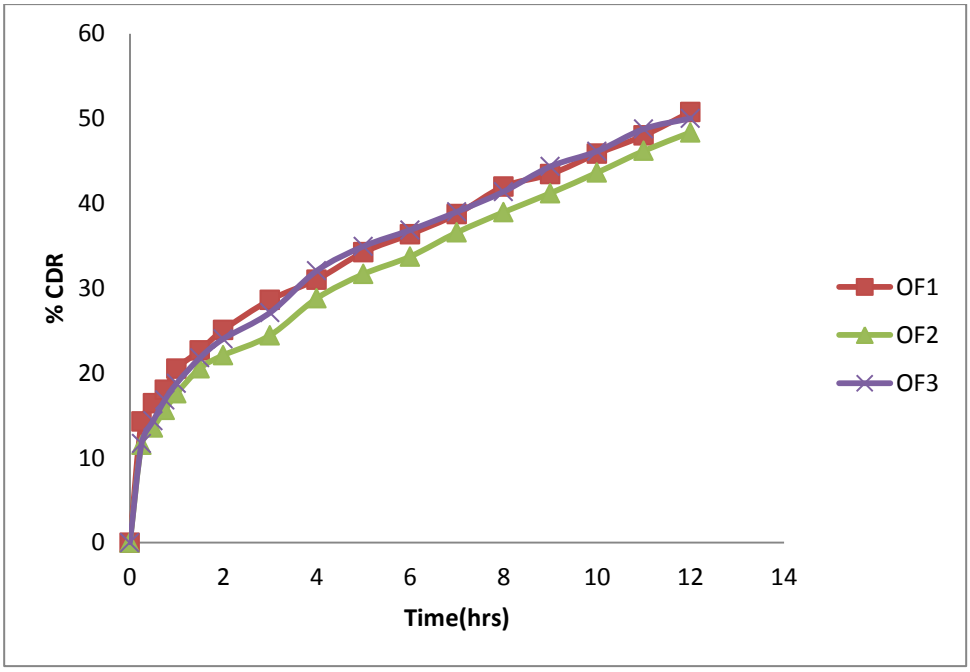

Figure 34 : *in vitro* drug release of pioglitazone (OF1 to OF3)

Comparative dissolution profile of OF4 to OF6 Formulations with Gum Olibanum

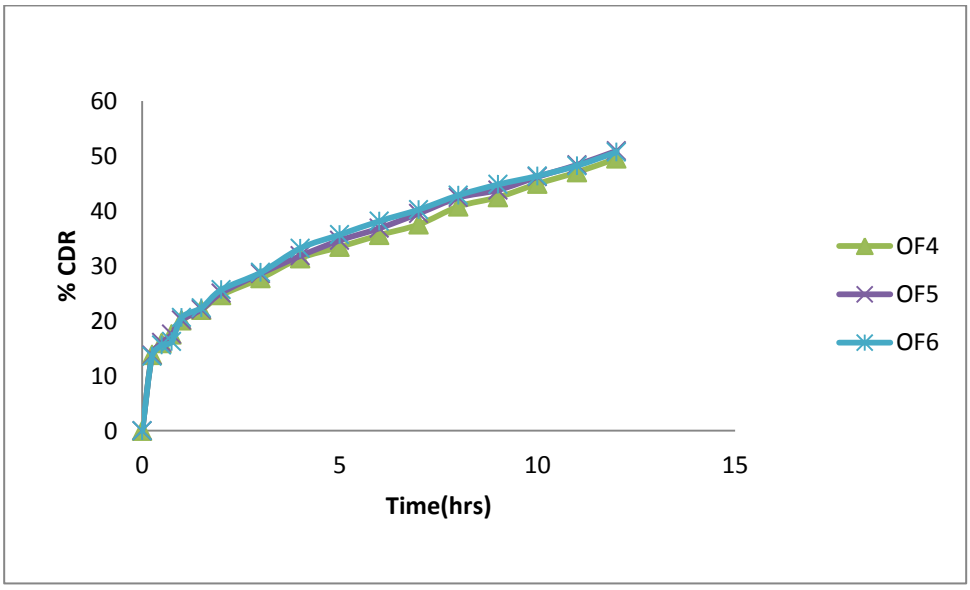

Figure 35 : *in vitro* drug release of pioglitazone (OF4 to OF6)

Comparative dissolution profile of OF7 to OF9 Formulations with Gum Olibanum

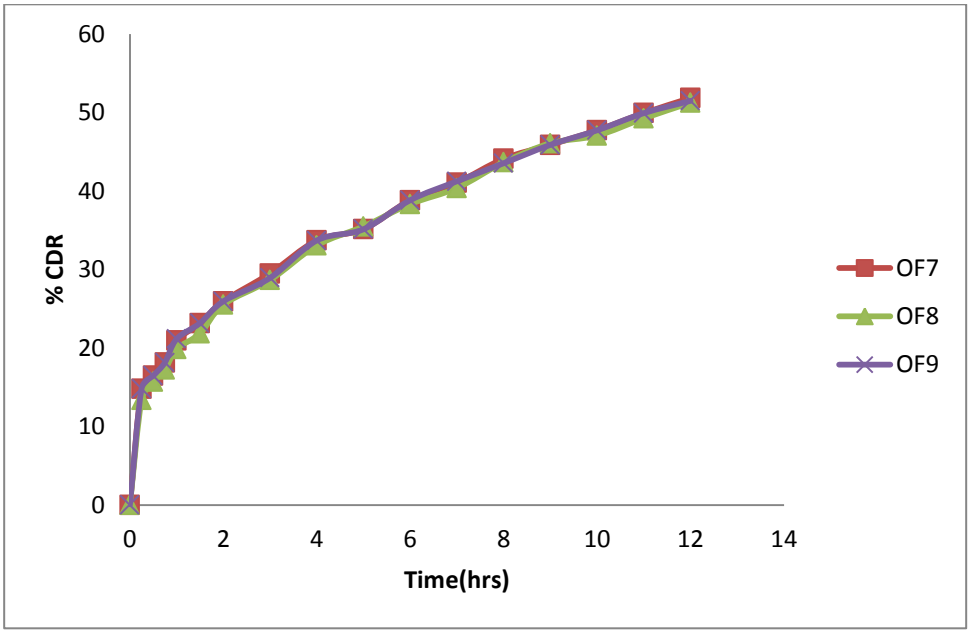

Figure 36: *in vitro* drug release of pioglitazone (OF7 to OF9)

ACCELERATED STABILITY STUDIES

Table 4.55: Accelerated stability studies

Parameters	Temperature maintained: 40 ^{0} C Relative humidity (RH) maintained: 75 ± 5% RH			
	0 (Initial)	1st month	2nd month	3rd month

Percentage yield (%)	96.8 ± 0.05	96.73 ± 0.13	96.8 ± 0.04	96.12 ± 0.06
In vitro wash off test	4hrs: 30min	4hrs:45min	4hrs: 25min	4hrs: 35min
In vitro drug release(%)	52.41 ± 0.05	52.37 ± 0.07	53.01 ± 0.12	52.56 ± 0.08

All the values are represented as mean ± SD (n =3)

RESULTS

1. Melting point of pioglitazone was determined by capillary method and found to be 183 ^{0}C. shown in table no:4.8.
2. FTIR studies were carried out on drug, excipients and drug-excipient samples. No new peaks were found and hence compatibility between the drug and the excipients was found. Peaks were found at the following wave numbers which are representative of specific functional groups. The IR interpretations of drug, excipients and drug and excipients were shown in the table nos: 4.9 to 4.17.

Optimization results

The 3% and 4% of sodium alginate were optimized based on the physical parameters. These were shown in the table no: 18.

- Xanthan gum 15% and 20% concentrations were optimized.
- Guar gum 5% and 10% concentrations were optimized.
- Gum kondagogu 10% and 15% concentrations were optimized.
- Gum olibanum 5% and 10% concentrations were optimized.

The above concentrations were optimized based on the physical parameters, swelling index, average particle size and mucoadhesion time data these were shown in table no: 20, 22 to 25.

The result of physical test of the formulations with different mucoadhesive agents like xanthan gum, guar gum, gum kondagogu, gum olibanum different formulations of pioglitazone hydrochloride microspheres were in the limits and comply with the standards shown in the table no: 4.35,4.37,4.39,4.41 respectively:

Xanthan Gum

- The results showed that the percentage yield in all experimental design formulations was found to contain in the range of 63.9% to 99% of pioglitazone hydrochloride.
- The results showed that the swelling index in all experimental design formulations was found to contain in the range of 370% to 510% of pioglitazone hydrochloride.
- The results showed that the avg. particle size in all experimental design formulations was found to contain in the range of 271.25µm to 415.3 µm of pioglitazone hydrochloride.
- The results showed that the mucoadhesion time in all experimental design formulations was found to contain in the range of 2h: 45min to 4h of pioglitazone hydrochloride.
- The results showed that the assay in all experimental design formulations was found to contain in the range of 94% to 97.8% of pioglitazone hydrochloride.

The above data were shown in the table no. 4.36

Guar gum

- The results showed that the percentage yield in all experimental design formulations was found to contain in the range of 79% to 96.8% of pioglitazone hydrochloride.
- The results showed that the swelling index in all experimental design formulations was found to contain in the range of 275% to 385% of pioglitazone hydrochloride.
- The results showed that the avg. particle size in all experimental design formulations was found to contain in the range of 145.4µm to 733µm of pioglitazone hydrochloride.
- The results showed that the mucoadhesion time in all experimental design formulations was found to contain in the range of 3h:30min to 5h of pioglitazone hydrochloride.
- The results showed that the assay in all experimental design formulations was found to contain in the range of 94% to 97.8% of pioglitazone hydrochloride.

The above data were shown in the table no. 4.38

Gum kondagogu

- The results showed that the percentage yield in all experimental design formulations was found to contain in the range of 95.4% to 97.74% of pioglitazone hydrochloride.
- The results showed that the swelling index in all experimental design formulations was found to contain in the range of 200% to 325% of pioglitazone hydrochloride.
- The results showed that the avg. particle size in all experimental design formulations was found to contain in the range of 342.2µm to 613.1µm of pioglitazone hydrochloride.
- The results showed that the mucoadhesion time in all experimental design formulations was found to contain in the range of 3h: 30min to 5h of pioglitazone hydrochloride.
- The results showed that the assay in all experimental design formulations was found to contain in the range of 94.7% to 98% of pioglitazone hydrochloride.

The above data were shown in the table no. 4.40

Gum olibanum

- The results showed that the percentage yield in all experimental design formulations was found to contain in the range of 93.7% to 97.6% of pioglitazone hydrochloride.
- The results showed that the swelling index in all experimental design formulations was found to contain in the range of 290% to 365% of pioglitazone hydrochloride.
- The results showed that the avg. particle size in all experimental design formulations was found to contain in the range of 344.2µm to 594.4µm of pioglitazone hydrochloride.
- The results showed that the mucoadhesion time in all experimental design formulations was found to contain in the range of 4h: 30min to 6h of pioglitazone hydrochloride.
- The results showed that the assay in all experimental design formulations was found to contain in the range of 95.4% to 97.4% of pioglitazone hydrochloride.

The above data were shown in the table no. 4.42

***In vitro* drug release studies**

Xanthan gum

The results showed that the *in vitro* drug release data of pioglitazone hydrochloride mucoadhesive microspheres formulations like XF1, XF2, XF3, XF4, XF5, XF6, XF7, XF8, XF9 was found to be 42.83%, 58.50%, 58.93%, 64.80%, 50.17%, 51.20%, 62.53%, 48.69%, 56.93% at the end of 12h respectively. These data were shown in table no: 4.43.

Guar gum

The results showed that the *in vitro* drug release data of pioglitazone hydrochloride mucoadhesive microspheres formulations like GF1, GF2, GF3, GF4, GF5, GF6, GF7, GF8, GF9 was found to be 37.62%, 36.20%, 32.18%, 33.87%, 39.95%, 40.52%, 39.48%, 45.71%, 40.83% at the end of 12h respectively. These data were shown in table no: 4.44.

Gum kondagogu

The results showed that the *in vitro* drug release data of pioglitazone hydrochloride mucoadhesive microspheres formulations like KF1, KF2, KF3, KF4, KF5, KF6, KF7, KF8, KF9 was found to be 46.42%, 48.39%, 50.81%, 48.35%, 52.13%, 51.00%, 51.56%, 52.41%, 51.40% at the end of 12h respectively. These data were shown in table no: 4.45.

Gum olibanum

The results showed that the *in vitro* drug release data of pioglitazone hydrochloride mucoadhesive microspheres formulations like OF1, OF2, OF3, OF4, OF5, OF6, OF7, OF8, OF9 was found to be 50.76%, 48.35%, 50.01%, 49.51%, 50.91%, 50.68%, 51.83%, 51.23%, 51.47% at the end of 12h respectively. These data were shown in table no: 4.46.

Kinetic data / model fitting analysis

Xanthan gum

XF9 is the best formulation it follows zero order the R^2 value is 0.98 and it follows fickian diffusion model the n value is 0.188.

Guar gum

GF8 is the best formulation it follows zero order the R^2 value is 0.97 and it follows non fickian dissolution model the n value is 0.502.

Gum kondagogu

KF8 is the best formulation it follows zero order the R^2 value is 0.998 and it follows fickian diffusion model the n value is 0.407.

Gum olibanum

OF9 is the best formulation it follows zero order the R^2 value is 0.980 and it follows fickian diffusion model the n value is 0.370.

Accelerated stability studies

Significant changes were not noticed. The formulation KF8 was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters and *in vitro* drug release data was shown in the table no: 4.55

DISCUSSIONS

FTIR spectra of the samples were compared with that of standard spectra of drug and excipients and found to have same peaks at particular wave numbers. No interference of peaks between drug spectra and drug excipients spectra was seen.

Compatibility between drug and excipient was studied by FTIR spectroscopy and found to have no incompatibility between drug and excipients.

In the swelling index study the polymers can be absorb phosphate buffer. Swelling index is may affect the mechanism of the drug release. Increase the swelling index to increase the drug release from the pioglitazone hydrochloride mucoadhesive microspheres.

The size of microspheres is depending upon concentration of sodium alginate used in the formulation. The increase in size of microspheres was observed with increase in concentration of sodium alginate. This could be due to increase in viscosity of the polymeric dispersion, which eventually lead to formation of bigger particle during orifice ionic gelation method.

In the formulations increases the concentration of mucoadhesive polymers which increases the mucoadhesion time and also increases the retardation time of the microspheres.

The release of drug depends upon the drug and polymer ratio. As the percentage of polymer increased, the drug release was decreased. Compared to all mucoadhesive polymers like xanthan gum, guar gum, gum kondagogu, gum olibanum. KF8 shows better drug release at 12h with compared to all formulations. So, gum kondagogu having more mucoadhesive property.

The release rate kinetics data for the K**F8** drug release was best explained by Zero-order equation, as the plots showed higher linearity ($r^2=0.988$), followed by Korsmeyer- Peppas ($r^2=0.712, n=0.407$) and Higuchi equation ($r^2=0.998$) and first order ($r^2=0.990$). As the drug release was best fitted in the Zero order kinetics and it follows fickian diffusion model indicating that the rate of drug release is concentration independent.

The stability of KF8 formulation was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on best formulation. The formulation was found to be stable, with no change in the percentage yield, mucoadhesion time and *In vitro* drug release pattern.

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