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Research Article

FORMULATION AND IN-VITRO EVALUATION OF SUSTAINED RELEASE ALGINATE BEADS OF INDOMETHACIN

Jharana Mallick[1]*, Debashrita Sahoo[2], Chandra Sekhar Sahoo[3] and Subash Chandra Dinda[4]

[1]Vision College of Pharmaceutical Sciences & Research, Boduppal, Uppal, Hyderabad- 500092, Andhra Pradesh, India.
[2]Caplin Point Laboratories, T. Nagar, Chennai, Tamil Nadu, India.
[3]Formulation & Development, Hetero Drugs, Hyderabad, Andhra Pradesh, India.
[4]Department of Pharmacy, Berhampur University, Odisha, India.

ABSTRACT

The purpose of this investigation is to prepare a novel drug delivery system of Indomethacin. Currently sustained release microspheres are one of the important categories of novel drug delivery system with sustained release behaviors. Indomethacin is a most widely used type of NSAID generally associated with disorders such as Rheumatoid arthritis, Osteo arthritis, Alkalysing spondylitis and all other types of Rheumatoid arthritis by its selective Cyclo oxygenase(cox)-2 inhibiting activity by providing symptomatic relief from pain and swelling. The Indomethacin microspheres were formulated by ion gelation technique and were capable of delaying onset of drug release for a prolonged period of 8-10 hours in the stimulated physiological environment of the body based on coating ratios of drug and sodium alginate. Dissolution studies demonstrate that the sodium alginate polymer coated formulation showed its action for 10hours at pH7.4. The Scanning Electron Microscopic study revealed the spherical shape and the presence of pores which is effective for loading of the dose. The X-Ray diffraction study showed a normal graph which represents no drug polymer interaction. Differential Scanning Calorimeter thermo gram analysis and FTIR spectroscopy also reveals no possibility of interaction between drug and polymers used in the study. The Qualitative tests like drug content, percentage yield, moisture content by karlfischer titration, bulk density, tapped density, carr's index were found. Effective data to confirm the formulation as an appropriate oral delivery system of sustained release action for a prolonged period of time for the effective treatment of Rheumatoid arthritis.

Keywords: Microsphere, Differential Scanning Calorimetry, X-ray diffraction study, SEM.

INTRODUCTION

Rheumatoid arthritis is an auto immune disease, which is chronic, affecting the people of all ethnic groups worldwide. Even though various categories like immuno suppresants, NSAID, steroidal anti inflammatory drugs are being used till now, the development of new anti rheumatic drugs is aimed towards the discovery of safe, potent drugs with minimal side effects. Here present study reveals the formulation and

evaluation of alginate beads of Indomethacin as an sustained release anti rheumatic drug delivery system.

To improve the sustained release activity of Indomethacin, the author tries to give it a form of novel drug delivery system by forming micro spheres in ion gelation technique. The in-vivo dissolution study and other parameters testing by different studies like Scanning Electron Microscope, Differential Scanning Calorimeter, X-Ray Diffraction etc helps to prove it a sustained release anti rheumatic drug delivery system.

EXPERIMENTAL METHODS

1. Collection of drug and polymer

The pure drug of Indomethacin was collected from Dr.Reddy's lab, Hyderabad. The sodium alginate used was Lobachem grade and all other chemicals used are in the Merck grade of lab reagent.

2. Formulation of alginate beads of Indomethacin

1%, 1.5 %, 2% & 2.5% w/v aqueous solution of sodium alginate was by a REMI stirrer of speed 500rpm to form a homogeneous polymer solution. The drug sample was dispersed in an appropriate proportion i.e. 1:1, 1:2 & 1:3 ratios and stirring was continued for one to two hours to allow complete dispersion. The dispersion was drop from a glass van syringe having 18-G hypodermic needle to the magnetically stirred calcium chloride water solution at a rate of 1ml per minute at stirring speed of 800 rpm. The beads are collected followed by washing and drying at 25ºc and relative humidity 30% [2].

3. Qualitative Evaluation

The formulations were quantitatively evaluated for different parameters like drug content, percentage yield, moisture content by Karl Fischer titration, bulk density, tapped density, Carr's index were evaluated.

4. Scanning Electron Microscopic (SEM) Study:

Scanning electron photo micro graphs of Indomethacin micro spheres were taken. A small amount of micro spheres were spread on glass stub[6]. After wards the stub containing the sample was placed in the in scanning electron microscope JSM 5610 LV SEM, JEOL, Datum Ltd (Japan) Chamber at accelerated voltage of 20kv, chamber pressure 0.6mm hg at different magnification[17].

5. X-Ray Diffraction (PXRD) study

The X-Ray diffraction study is important from the point of any conversion of crystallinity of the drug to the amorphous form which was carried out in Department of Instrumentation Science, Jadarpur University Calcutta.

6. Differential Scanning Calorimeter (DSC) Study

To study the drug polymer interaction in different ranges temperature, the author analyzed the formulation by Differential Scanning Calorimeter, carried out in Institution, Science, Jadarpur University which shows no interaction in form of independent graphs.

7. In-vitro dissolution study

In-vitro dissolution rate studies of the micro spheres were performed using USP XX type-II (electro lab TDP- 06T) apparatus[21]. Drug release was studied in 900ml of 7.2 pH phosphate buffer 37± 0.5ºC at 100 rpm. 1ml sample was withdrawn at regular intervals and the same quantity of pre warmed fresh dissolution medium was replaced. The samples withdrawn were assayed spectro photo metrically at 320nm using shimadzu 1700 UV visible spectrophotometer.

RESULTS AND DISCUSSION

The prepared Indomethacin micro spheres by ion gelation technique were discrete, spherical and free flowing having a good percentage yield. Scanning electron microscopy images demonstrated spherical shaped micro particles and presence of pores which gives the relevant idea of better drug absorption. Thermal behavior of Indomethacin micro spheres with sodium alginate by DSC shows no peak indicating no drug polymer interaction. The x-ray diffraction pattern of the pure 320drug shows peaks that are sharp and intense signifying its crystalline nature[10]. But its mixture with sodium alginate reduce the number of peaks and peak heights which suggest that the crystallinity converted to amorphous form and it is in good agreement with enhanced solubility. The in-vitro release data were plotted graphically by taking cumulative percent drug release versus time and the plots were found to obey kinetics of higuchi model[5] gives a very good bench marking anti rheumatic formulation of sustained release action[4].

Table 1: Formulation design of micro particles

Sl.no.	%w/v of formulation	Ratio (Drug: Sod. Alginate)	Distilled Water in ml.	Sodium Alginate (gm)	Drug(gm)
1	1	1:1	25	0.125	0.125
2	1	1:2	25	0.083	0.167
3	1	1:3	25	0.062	0.187
4	1.5	1:1	25	0.187	0.187
5	1.5	1:2	25	0.125	0.250
6	1.5	1:3	25	0.093	0.281
7	2	1:1	25	0.25	0.25
8	2	1:2	25	0.166	0.334
9	2	1:3	25	0.125	0.375
10	2.5	1:1	25	0.312	0.312
11	2.5	1:2	25	0.208	0.417
12	2.5	1:3	25	0.156	0.469

Table 2: Determination of % yield of Indomethacin

Sl. No.	Formulations	% w/v	Ratio (D:P)	% yield	Melting point in ºC	% incorporation	% Moisture content
1	Pure Ind.	-	-	-	172	-	1.1
2	Ind:Sod.alg	1	1:1	68.8	152	8.1	2.1
3	Ind:Sod.alg	1	1:2	73.2	149	7.2	2.5
4	Ind:Sod.alg	1	1:3	80.4	155	6.2	2.4
5	Ind:Sod.alg	1.5	1:1	82.133	156	7.1	2.2
6	Ind:Sod.alg	1.5	1:2	83.466	163	6.6	3.3
7	Ind:Sod.alg	1.5	1:3	87.2	165	5.7	3.1
8	Ind:Sod.alg	2	1:1	91.8	167	6.6	1.9
9	Ind:Sod.alg	2	1:2	94.4	163	5.6	2.3
10	Ind:Sod.alg	2	1:3	97.8	162	4.9	2.2
11	Ind:Sod.alg	2.5	1:1	94.88	164	5.8	2.5
12	Ind:Sod.alg	2.5	1:2	96.16	167	3.4	2.6
13	Ind:Sod.alg	2.5	1:3	97.28	165	3.5	2.4

Table 3: Determination of flow properties of Indomethacin

Formulation	% w/v	Ratio (D:P)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Packing factor
Pure Ind.	-	-	0.4312	0.5504	21.65	1.276
Ind:Sod.alg	1	1:1	0.4217	0.6606	36.13	1.565
Ind:Sod.alg	1	1:2	0.4314	0.6609	34.71	1.531
Ind:Sod.alg	1	1:3	0.4227	0.6507	35.02	1.539
Ind:Sod.alg	1.5	1:1	0.4195	0.6009	30.15	1.431
Ind:Sod.alg	1.5	1:2	0.3998	0.5012	20.23	1.253
Ind:Sod.alg	1.5	1:3	0.4718	0.6210	24.02	1. 316
Ind:Sod.alg	2	1:1	0.4277	0.5890	27.36	1.376
Ind:Sod.alg	2	1:2	0.4104	0.5995	31.49	1.459
Ind:Sod.alg	2	1:3	0.5002	0.6989	28.42	1.397
Ind:Sod.alg	2.5	1:1	0.4812	0.6019	20.03	1.250
Ind:Sod.alg	2.5	1:2	0.4514	0.6089	25.88	1.349
Ind:Sod.alg	2.5	1:3	0.4117	0.5993	31.31	1.456

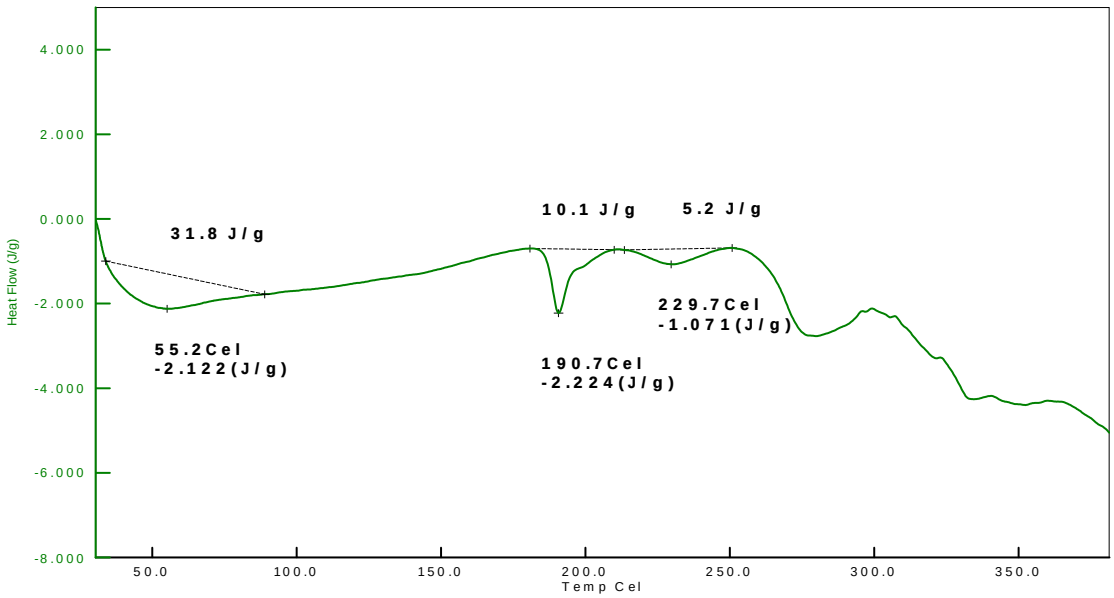


Fig. 1: DSC Photography of Indomethacin Microspheres

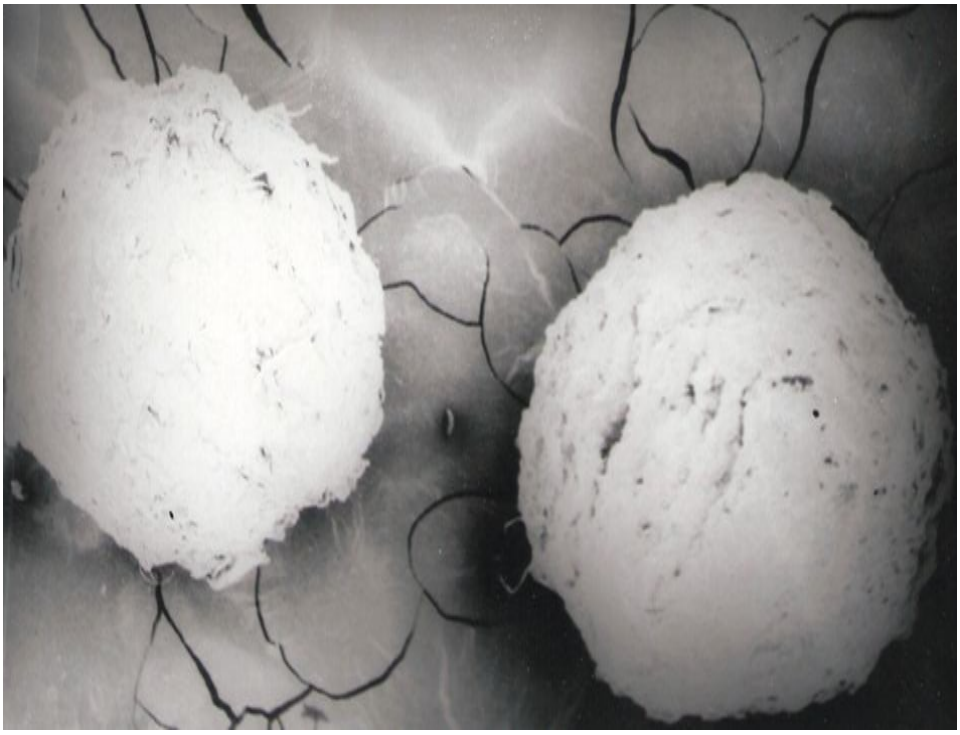
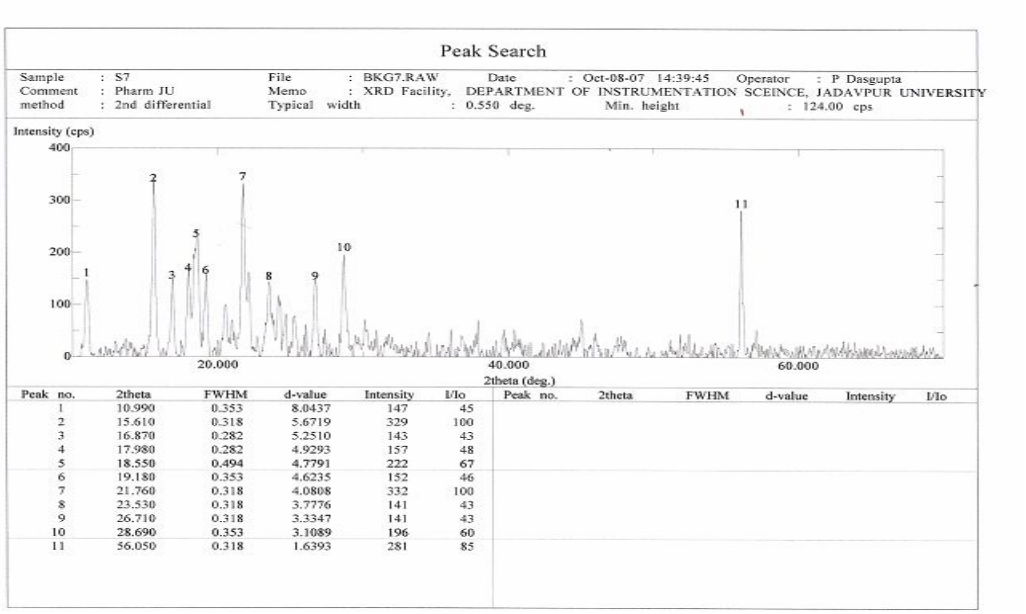


Fig. 2: SEM Photography of Indomethacin Microspheres



Peak Search

Sample : S7 File : BKG7.RAW Date : Oct-08-07 14:39:45 Operator : P Dasgupta
Comment : Pharm JU Memo : XRD Facility, DEPARTMENT OF INSTRUMENTATION SCEINCE, JADAVPUR UNIVERSITY
method : 2nd differential Typical width : 0.550 deg. Min. height : 124.00 cps

Intensity (cps)

2theta (deg.)

Peak no.	2theta	FWHM	d-value	Intensity	I/Io	Peak no.	2theta	FWHM	d-value	Intensity	I/Io
1	10.990	0.353	8.0437	147	45						
2	15.610	0.318	5.6719	329	100						
3	16.870	0.282	5.2510	143	43						
4	17.980	0.282	4.9293	157	48						
5	18.550	0.494	4.7791	222	67						
6	19.180	0.353	4.6235	152	46						
7	21.760	0.318	4.0808	332	100						
8	23.530	0.318	3.7776	141	43						
9	26.710	0.318	3.3347	141	43						
10	28.690	0.353	3.1089	196	60						
11	56.050	0.318	1.6393	281	85						

Fig. 3: X-RD Photography of Indomethacin Microspheres

DISSOLUTION DATA OF INDOMETHACIN (1:1)

IME IN	SQRT	CR	% MR	ARA	% ARA	Log(% ARA)	W01/3-W1/3
0.25	0.5	0.6434	3.217	19.3566	96.783	1.98579908	0.177441862
0.5	0.707107	1.5266	7.633	18.4734	92.367	1.965516838	0.192781407
1	1	3.6714	18.357	16.3286	81.643	1.911918955	0.199414501
2	1.414214	3.9658	19.829	16.0342	80.171	1.904017301	0.203854313
3	1.732051	4.092	20.46	15.908	79.54	1.900585587	0.206082769
4	2	4.1761	20.8805	15.8239	79.1195	1.898283534	0.210546281
5	2.236068	4.2182	21.091	15.7818	78.909	1.89712654	0.217274213
6	2.44949	4.3023	21.5115	15.6977	78.4885	1.894806029	0.228561485
7	2.645751	4.4285	22.1425	15.5715	77.8575	1.891300454	2.714417617
8	2.828427	4.6387	23.1935	15.3613	76.8065	1.885397975	2.714417617

T.M.C. = 20 mcg per ml.

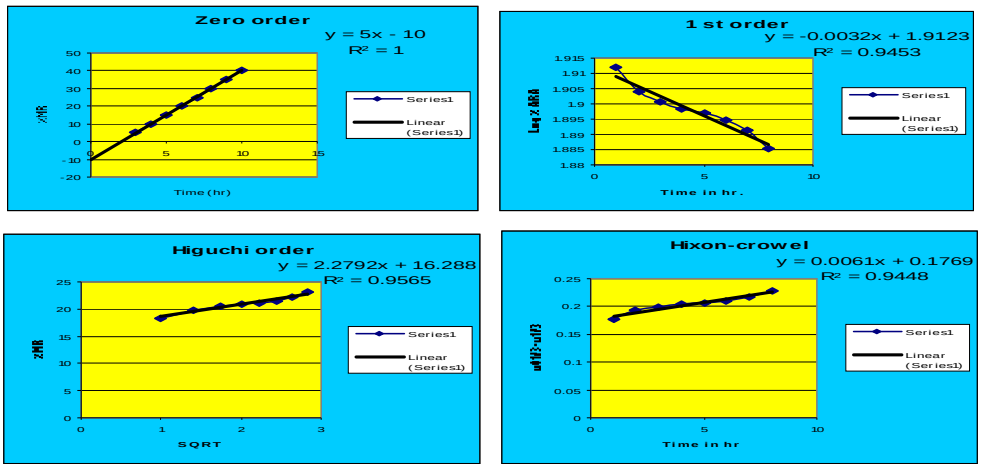


Fig. 4a: Dissolution Profile of Indomethacin Microspheres

DISSOLUTION DATA OF INDOMETHACIN (1:2)

TIME IN hr	SQRT	CR	% MR	ARA	% ARA	Log (%ARA)	W01/3-W1/3
0.25	0.5	0.5173	2.5865	19.4827	97.4135	1.988619148	0.023607525
0.5	0.707107	1.3163	6.5815	18.6837	93.4185	1.97043289	0.060906192
1	1	3.3771	16.8855	16.6229	83.1145	1.919676797	0.162290723
2	1.414214	3.503	17.515	16.497	82.485	1.916374979	0.168750233
3	1.732051	3.587	17.935	16.413	82.065	1.914157974	0.173078294
4	2	3.7556	18.778	16.2444	81.222	1.909673679	0.181810099
5	2.236068	3.7976	18.988	16.2024	81.012	1.908549354	0.183994674
6	2.44949	3.8397	19.1985	16.1603	80.8015	1.907419423	0.186188242
7	2.645751	3.881	19.405	16.119	80.595	1.9063081	0.188343832
8	2.828427	4.007	20.035	15.993	79.965	1.902899942	0.194943047
9	3	4.007	20.035	15.993	79.965	1.902899942	0.194943047

T.M.C. = 20 mcg per ml.

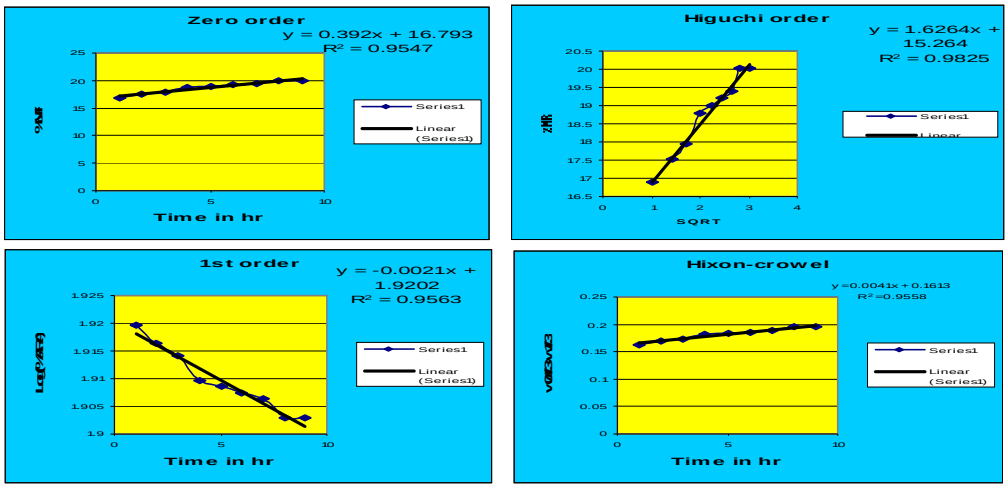


Fig. 4b: Dissolution Profile of Indomethacin Microspheres

DISSOLUTION DATA OF INDOMETHACIN (1:3)

TIME IN hr	SQRT	CR	% MR	ARA	% ARA	Log (% ARA)	W01/3-W1/3
0.25	0.5	0.4332	2.166	19.5668	97.834	1.99048981	0.019741321
0.5	0.707107	0.9799	4.8995	19.0201	95.1005	1.9781828	0.045075337
1	1	3.6714	18.357	16.3286	81.643	1.911918955	0.177441862
2	1.414214	3.9658	19.829	16.0342	80.171	1.904017301	0.192781407
3	1.732051	4.007	20.035	15.993	79.965	1.902899942	0.194943047
4	2	4.176	20.88	15.824	79.12	1.898286279	0.203849024
5	2.236068	4.218	21.09	15.782	78.91	1.897132043	0.206072173
6	2.44949	4.3023	21.5115	15.6977	78.4885	1.894806029	0.210546281
7	2.645751	4.6387	23.1935	15.3613	76.8065	1.885397975	0.228561485
8	2.828427	4.807	24.035	15.193	75.965	1.880613542	0.237673276
9	3	4.849	24.245	15.151	75.755	1.879411303	0.239957645

T.M.C. = 20 mcg per ml.

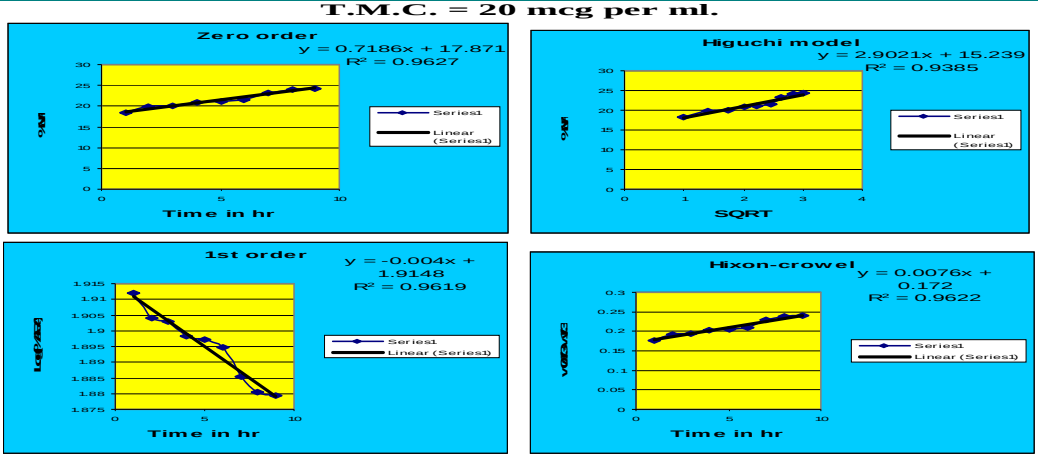


Fig. 4c: Dissolution Profile of Indomethacin Microspheres

CONCLUSION

It could be concluded that the sustained release alginate beads of Indomethacin evaluated by qualitative method gave effective data's.

Extensive and intensive experimental datas with regard to the percentage yield, drug content, melting point, moisture content by auto Karl Fischer titration and flow ability obtained such that the physiability of pilot plant study with regard to scale of technique is quite encouraging.

The surface topography by SEM under high magnification shows nearly circular shape with several surface pores through which the drug find a gateway for releasing to the dissolution media or invivogartric fluid.

From the Differential Scanning Calorimeter pattern of thermal degradation of compound reveals no interaction as evidenced by their appearance of new peaks. The In-vitro dissolution study conducted for a period of 12hours in continuous monitoring process shows diffusion rate controlled kinetics following Higuchi model.

The In-vitro dissolution release pattern follows Higuchi model and their activity is sustained over a maximum period of 10 hours which shows 2 times administration of the formulation would be ideal for pain management of rheumatoid arthritis. Similarly the SEM, X-Ray Diffraction studies and Differential Scanning Calorimeter studies also helped for showing no drug polymer interaction and spherical shape of the micro sphere.

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