World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

FORMULATION AND EVALUATION OF ENTERIC COATED MICROSPHERES OF ASPIRIN

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Article history:

Received: February 4th 2022
Accepted: March 4th 2022
Published: April 19th 2022

Abstract:

Microspheres are the substances or compounds which having free flowing property (powders). Microspheres are consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size from 1-1000µm. A 2% sodium alginate solution dissolving 100 ml distilled water with stirring on a magnetic stirrer. Weighed amount of Aspirin was dispersed in the sodium alginate solution crosslinking solutions of various concentration (10%, 15%, 20%) w/v were prepared by dissolving calcium chloride in distilled water. coating with 2% Hydroxyl Propyl Methyl Cellulose Phthalate (HPMCP) in water. Thus it can be concluded that all the coated microspheres prolonged and extended the drug release. Therefore, these coated microspheres can be used to control and prolong the drug release effectively and reducing the dosing frequency of Aspirin

Keywords: Microspheres, Sodium alginate, Calcium chloride, Hydroxyl propylmethyl cellulose phthalate

INTRODUCTION:

1.1. MICROSPHERES

Microspheres are free flowing polymeric micro particles loaded with biologically active drugs intended for providing constant and prolonged therapeutic effect thus reducing the dosing frequency and thereby improving the patient compliance. They not only used for prolonged releasebut also for targeting drug to specific site for minimizing the side effects. Coating of microspheres with a suitable coating material is an additional important technique in microsphere formulation taken for modification of characteristics of microspheres especially in-vitro release profile.[1,2]
Microspheres are the substances or compounds which having free flowing property (powders). Microspheres are consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size from 1-1000µmThere are two types of microspheres;

- Microcapsules
- Micrometrics

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micrometrics in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporation a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified naturalproducts.[3,4,5]

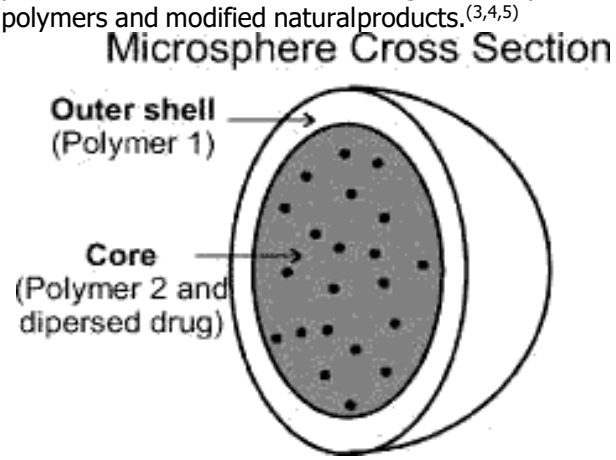

Fig.no:1 Microsphere

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

MATERIALS AND METHODS

S. No	CHEMICAL /MATERIAL	SOURCE
1	Aspirin	OXFORD LAB FINE CHEM LLP
2	Sodium alginate	Spectrum chemicals Ltd
3	Calcium chloride	Spectrum chemical Ltd
4	Distilled water	Spectrum chemical Ltd
5	Hydroxy propyl Methyl CellulosePhthalate	Global scientific company

Table 1 : LIST OF MATERIALS

PREPARATION OF STOCK SOLUTION PREPARATION OF SOLUTIONS FOR CALIBRATION CURVE

Stock solution 1:

Stock solution of drug (1mg/ml) is prepared by dissolving 100 mg of drug in 100 ml solution of methanol and phosphate buffer pH 6.8 in 100 ml volumetric flask (to get 1000 µg/ml drug solutions) with vigorous shaking and further sonicated for about 10 minutes.

Stock solution 2:

10 ml of this (stock solution 1) is diluted to 100ml with phosphate buffer pH 6.8 to get a stock solution containing 100 µg/ml of drug.

Stock solution 3:

1ml of this (stock solution 2) is diluted to 10 ml with phosphate buffer pH 6.8 to get a stock solution containing 10 µg/ml of drug.

Preparation of sample solution

Different dilution of stock solution with phosphate buffer pH 6.8 were made to obtain solution have in concentration 2, 4, 6,8,10, µg/ml. absorbance was measured at 245nm space against phosphate buffer pH 6.8 as blank, using UV spectrophotometer. Standard curve was plotted with concentration on X-axis and absorbance on Y-axis.[7,8]

FORMULATION OF ENTERIC COATED MICROSPHERES OF ASPIRIN

The microspheres of Aspirin were prepared by Ionotropic gelation method using sodium alginate as polymer and calcium chloride as cross linking agent. A 2% sodium alginate solution was prepared by dissolving weighed amount of sodium alginate in 100 ml distilled water with stirring on a magnetic stirrer. Weighed amount of Aspirin was dispersed in the sodium alginate solution cross linking solutions of various concentration (10%, 15%, 20%) w/v were prepared by dissolving calcium chloride in distilled water .Sodium alginate solution was filled in the syringe and dropped into the solution of cross linking agent from a height of 6 inches with speed of about 50 drops per minute. Microspheres were prepared due to the cross linking of the cross linking ofthe polymer by the calcium ions.

The prepared microspheres were collected by decantation followed by centrifugation of the solution, air dried overnight and then stored in vacuum desiccators. For the coating of prepared microspheres a fraction of uncoated microspheres were subjected to the process of coating with 2% Hydroxyl Propyl Methyl Cellulose Phthalate (HPMCP) in water.

The prepared microspheres were dipped into the enteric coating solution for 30 minutes and collected by decantation followed by centrifugation ,air dried for overnight and then stored in microspheres prepared with different concentration (10,15,20%) of cross linking agent were coded as formulation F1, F2 and F3.[9,10,11]

World Bulletin of Public Health (WBPH)
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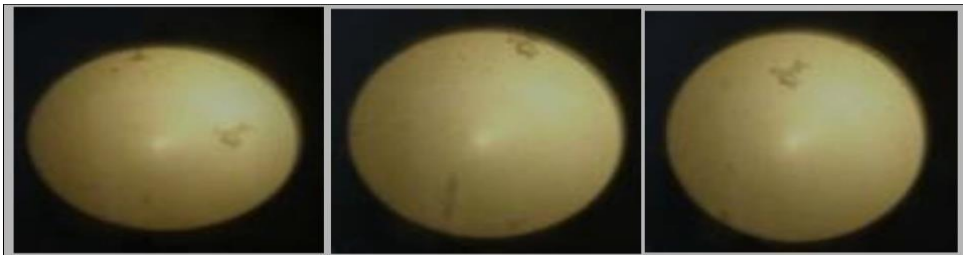
Volume-9, April 2022
ISSN: 2749-3644

Step.1. Dissolve 1 gm of sodium Alginate in 50ml water with 1gm of Aspirin

Step. 2. Addition of polymer mixture (Internal phase)

Step 3. Filtration of microspheres after washing

Step 4. Microspheres was focused at 10x lens to visible themoveable microsphere



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ISSN: 2749-3644

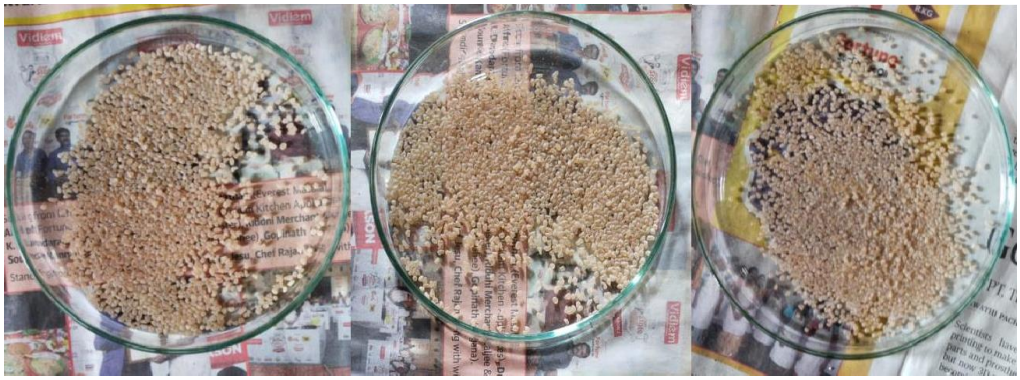

Figure No.2.Preparation of Microsphere

FORMULATION OF MICROSPHERES

FORMULATIONS	ASPIRIN (mg)	SODIUM ALGINATE % (w/v)	CALCIUM CHLORIDE % (w/v)	HYDROXY PROPYL METHYL CELLOSE PHTHALATE (HPMCP) %
F1	500mg	2%	10%	2%
F2	500 mg	2%	15%	2%
F3	500 mg	2%	20%	2%

Table no: 2 Formulation of microspheres

MICROSCOPE BASED MICROSPHERES

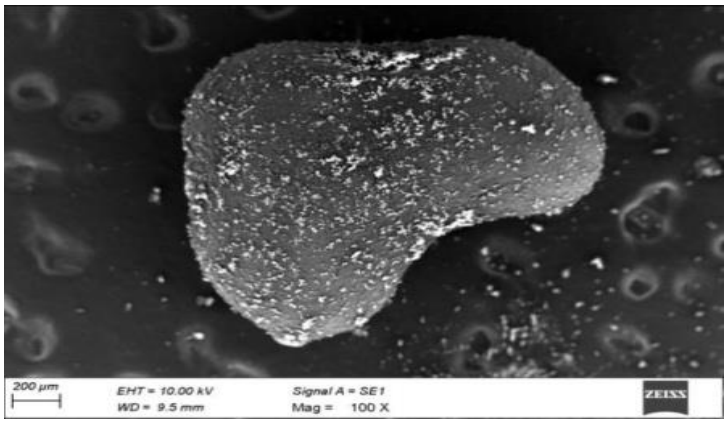

FIGURE NO: 3 MICROSCOPE OF MICROSPHERES

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
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EVALUATION OF ENTERIC COATED MICROSPHERES OF ASPIRINMICROMERITICS PROPERTIS [12,13]

1. **Bulk density:** A weighed amount of microspheres were filled into a measuring cylinder and thevolume (Vo) occupied by the microspheres was noted and the bulk density was calculated as followed
2. **Bulk Density = Mass of the microspheres (W) / Bulk volume of the microspheres (Vo).**
3. **Tapped density:** A weighed quantity of microspheres was filled in a measuring cylinder and the cylinder was tapped against a wooden surface at regular interval for 100 times, then the volumeoccupied by the microspheres was noted down and tapped density was calculated as followed.
4. **Tapped Density = Mass of the microspherese (W) / Tapped Volume of the microspheres (Vf).**
5. **Flow properties:** Carr's compressibility index and Hausner's ratio were calculated for the uncoated microspheres using the following equations.
6. **Carr's index:** Carr's index was determined using bulk density and tapped density.

   Carr's index= Tapped density- Bulk density / Tapped density× 100
7. **Hausner's ratio:** Hausner's ratio is used for predicting the flow characteristics.
8. **Hausner's ratio = Tapped density/ Bulk Density**
9. **Angle of repose:** It is a measure of resistance to flow and calculated by funnel method. Weighedquantity of microspheres was passed through the funnel and the heap was formed on the paper. The area of the heap was encircled and diameter of the circle and the height of the heap were measured and the angle of repose was calculated as followed.

$$\Theta = \tan^{-1} (h/r)$$

Where,

Θ= the angle of repose
h = height of pile
r = radius of base of the pile

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Volume-9, April 2022
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Drug content:

An amount of microspheres containing a quantity equivalent to 100 mg Aspirin were weighed, crushed after 8 hrs diluted appropriately and analyzed spectrophotometerically at 245 nm for determination of the drug content.

***In-vitro* drug release study:**

In-vitro release study of the microspheres was carried out using USP rotating basket method A weighed amount of microspheres was placed in the basket, and then put into the 900ml dissolution medium of phosphate buffer pH 6.8 (after 8h) at maintained 37 ± 0.5°C with a paddle rotation speed of 50 rpm. At 1,2,3,4,5,6,7, and 8h, 5ml Samples were withdrawn at Different intervals and an equal volume of the fresh dissolution medium was introduced into the apparatus. Each sample was diluted suitably with dissolution medium and analyzed with UV spectrophotometer at 245 nm for determining the drug release.

SEM Analysis:

The surface morphology of the formulated beads was analyzed by scanning electron microscope (SEM) (Carl ZEISS EVO 18-Germany)-operating modes secondary electron (SE) and Backscattered electron (BSD) modes. Up to 200 nm resolution depends up on sample. it is attached with AMETEK Team V.4.3 EDS detector.

DRUG RELEASE KINETIC STUDY

Drug Release Kinetics

Drug release kinetics was performed using model dependent method in which the dissolution profile of each formulation has been subjected various kinetics like zero order, first order, Higuchi's and korsmeyer-Peppasmodel.[14,15,16]

The data obtained from in vitro drug release studies were plotted in various kinetic models; as mentioned below zero order (Equation 1) as cumulative amount of drug released vs time, first order(Equation 2) as log as cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3)as cumulative percentage of drug released vs square root of time.

$$Qt = Q0+k0t$$

(Equation 1)

Where Q_t is the amount of drug dissolved in time t,Q_0 is the initial amount of drug in the solution and K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$LogC = logCO-kt/2.303$$

Where C_0 is the initial concentration of drug is the first order constant, and t is the time.

$$Qt=KHt^{1/2}$$

Where K_H is the constant reflecting the design variables of the system and t is the time in hours. Hence drug release rate is proportional to the reciprocal of the square root of time. Drug release were plotted in kors meyer equation (Equation 4) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty=Kt^n$$

Where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant.constant.

World Bulletin of Public Health (WBPH)
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Volume-9, April 2022
ISSN: 2749-3644

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

Table 4: Diffusion Exponent and Solute Release Mechanism

9. RESULTS AND DISCUSSION

Standard calibration curve for Aspirin:

The UV Spectrophotometric method was used to analyze Aspirin. The absorbance of thedrug in phosphate buffer saline (pH 6.8) was measured at a wavelength of 245nm.

S.No	Concentration	Absorbance at 245 nm
1	0	0
2	2	0.11
3	4	0.016
4	6	0.027
5	8	0.032
6	10	0.040

Table 5: Standard calibration curve for Aspirin

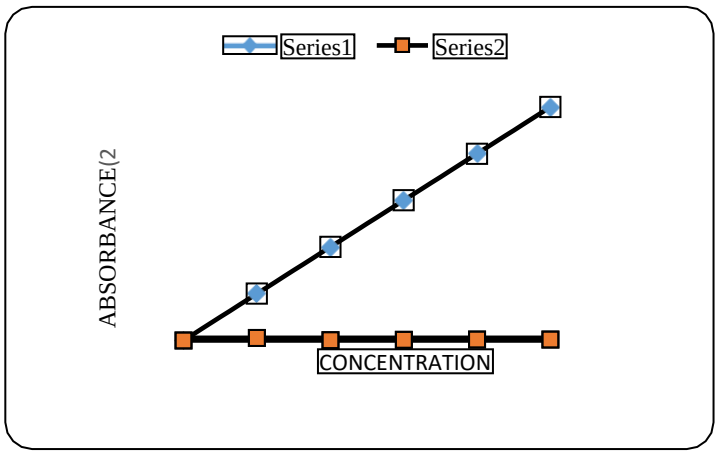

Figure No 3: Standard calibration curve

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

MICROMERITIC PROPERTIES

Flow properties:

Formulation	k density (g/ml)	Tapped density (g/ml)	Angle of repose (0)	Carr's index	usner'sratio
F1	0.629	0.733	7.025	24.8	1.232
F2	1.169	1.328	7.363	22.0	1.185
F3	0.839	0.870	11.209	6.1	1.057

Table 6: Flow properties of Aspirin microspheres

Bulk Density:

The bulk density was found in the range of 0.629 to 1.169 g/ml

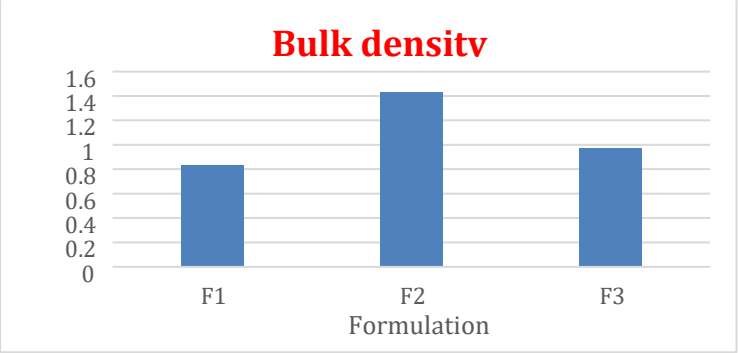

Figure No 4: Bulk density

Tapped Density:

The tapped density was found in the range of 0.733 to 1.328 g/ml.

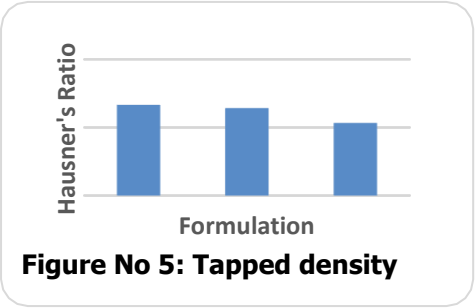

Figure No 5: Tapped density

Hausner's ratio:

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

The Hausner's ratio of the formulation was found in the range of 1.057 to 1.232 g/ml.

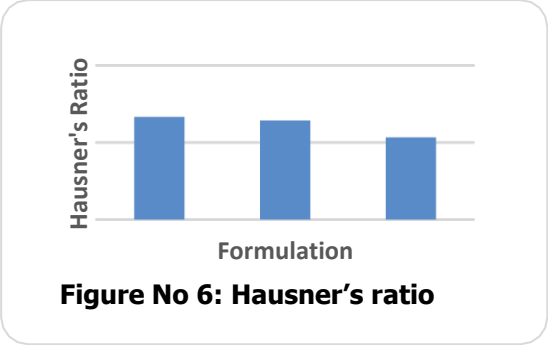

Figure No 6: Hausner's ratio

Carr's index:
The Carr's index of the formulation was found in the range of 6.1 to 24.8 g/ml.

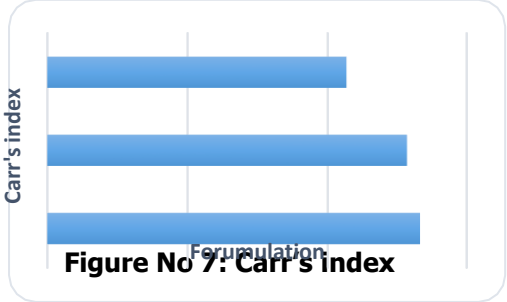

Figure No 7: Carr's index

Angle of repose:
The angle repose was found in the range of 7.025 to 11.209. The flow property of themicrospheres was found to be excelled flow.

Inference:
The flow properties of the formulated microspheres were evaluated. The flow property wasfound to be excelled flow.

Drug content:
The drug content for diffident microspheres formulation was in the range of 93.20 to 95.80%.

S.NO	FORMULATION	DRUG CONTENT
1	F1	93.20
2	F2	95.80
3	F3	94.40

Table 7: drug content of enteric coated microspheres

Inference:
Microspheres formulation F2 (15% $Cacl_2$ cross linking agent) showed highest drugcontent of 95.80%

***IN-VITRO* DISSOLUTION STUDY**

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Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

Time in hours	%CDR		
	F1	F2	F3
0	0	0	0
1	3.40	14.10	2.15
2	14.58	24.12	8.20
3	30.60	36.20	15.21
4	40.70	45.60	30.60
5	50.20	57.25	55.70
6	58.10	65.18	57.65
7	60.70	75.60	65.80
8	65.55	86.25	75.60

Table 8: *IN-VITRO* DISSOLUTION STUDY

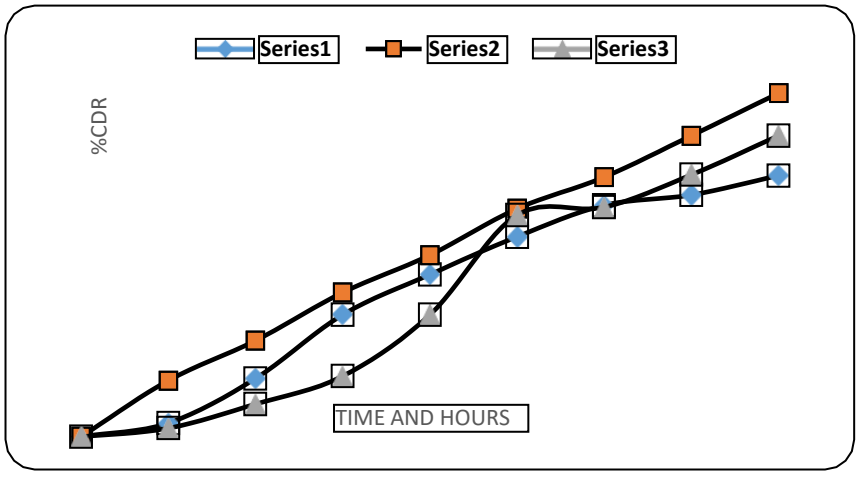

Figure No 8: *IN-VITRO* DISSOLUTION STUDY

Drug release kinetics

The release profile obtained from the best optimized formulation was fitted to variouskinetic equation to know the mechanism of drug release as indicated by the maximum r^2 value

Log T	T	%DR	MAINDR	% LOG CUMU DR	SQRT T	LOG % DR
0.0	0	0.00	100	2	0.00	0.00
0.0	1	8.10	91.9	1.96	1.00	0.91
0.3	2	17.20	82.8	1.92	1.41	1.24

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

0.5	3	24.63	75.37	1.88	1.73	1.39
0.6	4	36.13	63.87	1.81	2.00	1.56
0.7	5	51.21	48.79	1.69	2.24	1.71
0.8	6	63.17	36.83	1.57	2.45	1.80
0.8	7	73.62	26.38	1.42	2.65	1.87
0.9	8	82.26	17.74	1.25	2.83	1.92

Table 9: Mechanism of release kinetic

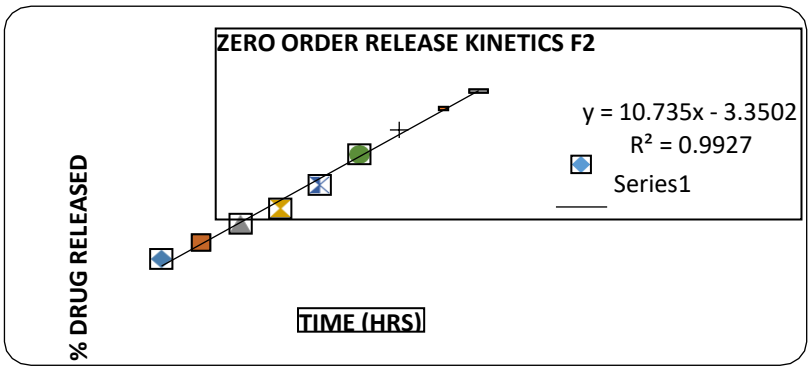

Figure No 9: zero order kinetics of enteric coated microspheres

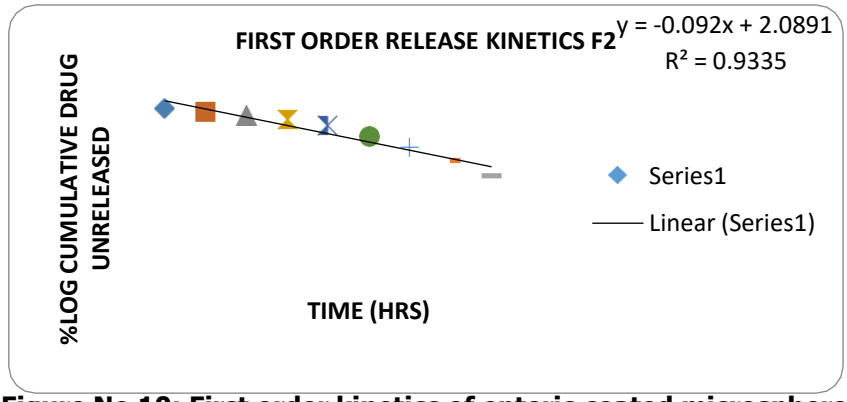

Figure No 10: First order kinetics of enteric coated microspheres

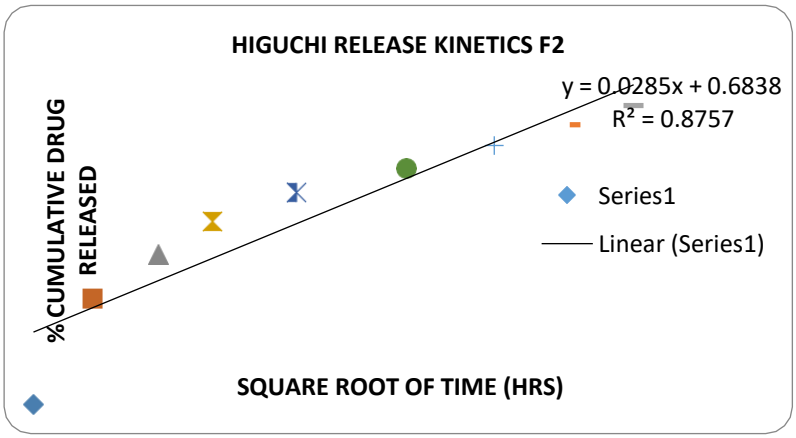

Figure No 11: Higuchi order kinetics of enteric coated microspheres

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Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

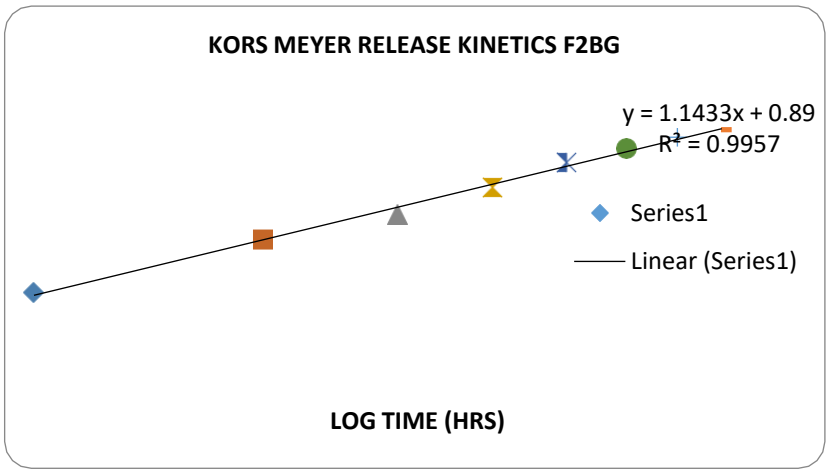

Figure No 12: Kors meyer order kinetics of enteric coated microspheres

From the release kinetic data the optimized formulation was fitted with various kinetics equations. From the graphical representation it can be understood that this layer is best fit into Zero Order kinetics which has shown a regression coefficient (r^2) of 0.992 and Higuchi model (r^2=0.933) and Peppas equation was used to analyze the pattern of the formulation and the value of "n" was found to be 0.45< n < 0.89, indicating the drug release follows Non-Fickian diffusion.

Formulation	Model	R^2	Slope	K
F2	Zero Order	0.992	10.73	3.350
	First Order	0.933	0.092	2.089
	Higuchi Model	0.875	0.028	0.683
	Korsmeyer Model	0.995	1.143	0.89

Table 10: Kinetics analysis of dissolution data for formulation

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-9, April 2022
ISSN: 2749-3644

SUMMARY AND CONCLUSION

- Aspirin drug is selected based on literature survey.
- Enteric coated polymer was selected based on literature survey.
- Trail batches of enteric coated microspheres of Aspirin were prepared by inotropic method.
- Micromeritics results of microspheres showed that they have good flow property.
- Various evaluation parameters were done for all the three formulations such as percentage of drug content, *In-vitro* drug release studies, SEM analysis study and drug release kineticsstudy.
- Among all three formulations, Formulation 2 (F2) showed maximum percentage drug release at 8 hours. So the formulation 2 (F2) is selected as optimized formulation.
- From the In-vitro drug release data of F2 was fitted with various kinetic equations and it follows non-fickian diffusion.
- Thus it can be concluded that all the coated microspheres prolonged and extended the drug release. Therefore, these coated microspheres can be used to control and prolong the drug release effectively and reducing the dosing frequency of Aspirin.

AKNOWLEDGEMENT

We sincerely express our deep sense of gratitude to The management, Sree Abirami Institutions and Charitable Trust for providing the required facilities regarding this research and also for this support. We are highly indepted to Dr. M. Senthil Kumar, Principal, Sree Abirami College of Pharmacy who is our inspiration to pursue this undertaking. We are also obliged to our colleagues. This work would not have been possible without there worthy experience enormous help.

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