आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

NAAC ACCREDITED

E-Content

IFTM University, Moradabad

STUDIES ON SUSTAINED RELEASE FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEM

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Introduction

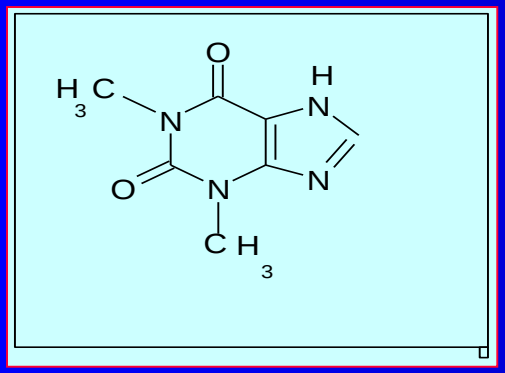
- Sustained or Controlled Drug Delivery
- Gastroretentive Drug Delivery System
- Floating Or Hydrodynamically balanced System
- Multiparticulate or Multiple unit or Floating Microsphere or Microballoons
- Novel Oral Drug Delivery System

Aim & Objective

- To Formulate Gastroretentive floating microsphere of theophylline as model drug.
- Physical Characterization and in vitro drug release
- Buoyancy and drug incorporation efficiency.
- To study effect of polymer combination and concentration on drug release.
- To Study Stability for microballoons and dosage form.

DRUG AND EXCIPENT PROFILE

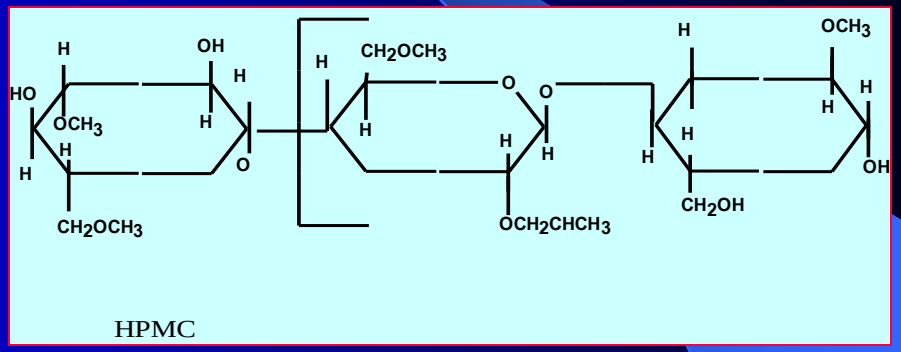
THEOPHYLLINE



$C_7H_8N_4O_2$ Mol. Wt. 180.17 (anhydrous)

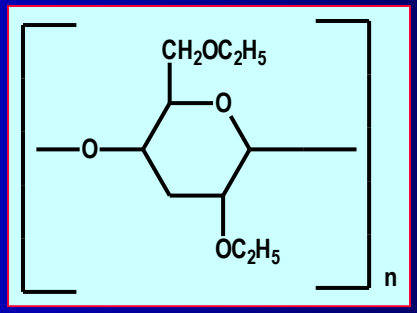
Category: Xanthine bronchodilator

HPMC



Molecular weight: Approx. 86,000

ETHYL CELLULOSE



PLAN OF WORK

- LITERATURE SURVEY
- PROCUREMENT OF SAMPLE AND SCREENING
- MATERIAL AND EQUIPMENT
- EXPERIMENTAL WORKDONE
- RESULT AND DISCUSSION
- REFERENCE

MATERIAL AND EQUIPMENT

S. No.	MATERIALS	GRADE	SUPPLIED BY
1	Theophylline anhydrous	IP	Natco Pharma Ltd. , Hyderabad
2	Ethyl cellulose or Surelease	USP EP	Colorcon Pvt. Ltd. Goa
3	HPMC K100LV	USP EP	Colorcon Pvt. Ltd. Goa
4	HPMC K4 , K!5	USP EP	Colorcon Pvt. Ltd. Goa
5	CycloHexane	AR	Research Lab. Fine chem. Mumbai
6	Methanol	AR	Loba Chemie, Mumbai
7	Ethanol	LR	Changshu Yangyun Chemical
8	Methyl cellulose	AR	Merck Ltd. Mumbai
9	Tween 20	AR	Merck Ltd. Mumbai
10	Tween 80	AR	Merck Ltd. Mumbai

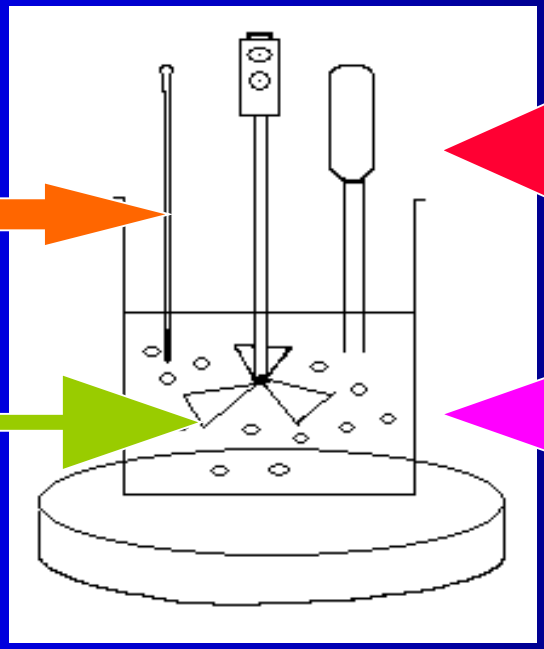
S. N.	EQUIPMENT	SUPPLIED BY
1	Mechanical stirrer (medium duty)	Remi Motors
2	Hot Plate with magnetic stirrer	---------
3	Single pan digital balance	Afcoset
4	UV-visible spectrophotometer single beam	Milton Roy
5	Dissolution test apparatus (six stage)	Electrolab
6	Microscope	Intel
7	Suction Pump	----------
8	pH Meter	Hanna Instruments
9	Hot air oven	Kumar Industries
10	B.O.D. Incubator	Kumar Industries, Mumbai.

EXPERIMENTAL WORKDONE

PREPARATION OF FLOATING MICROSPHERE

Thermometer

300-500 RPM



Drug : Polymer
In
Ethanol : DCM

MICROBALLOONS

Heating at 30-40 o C

MICROMERITICS

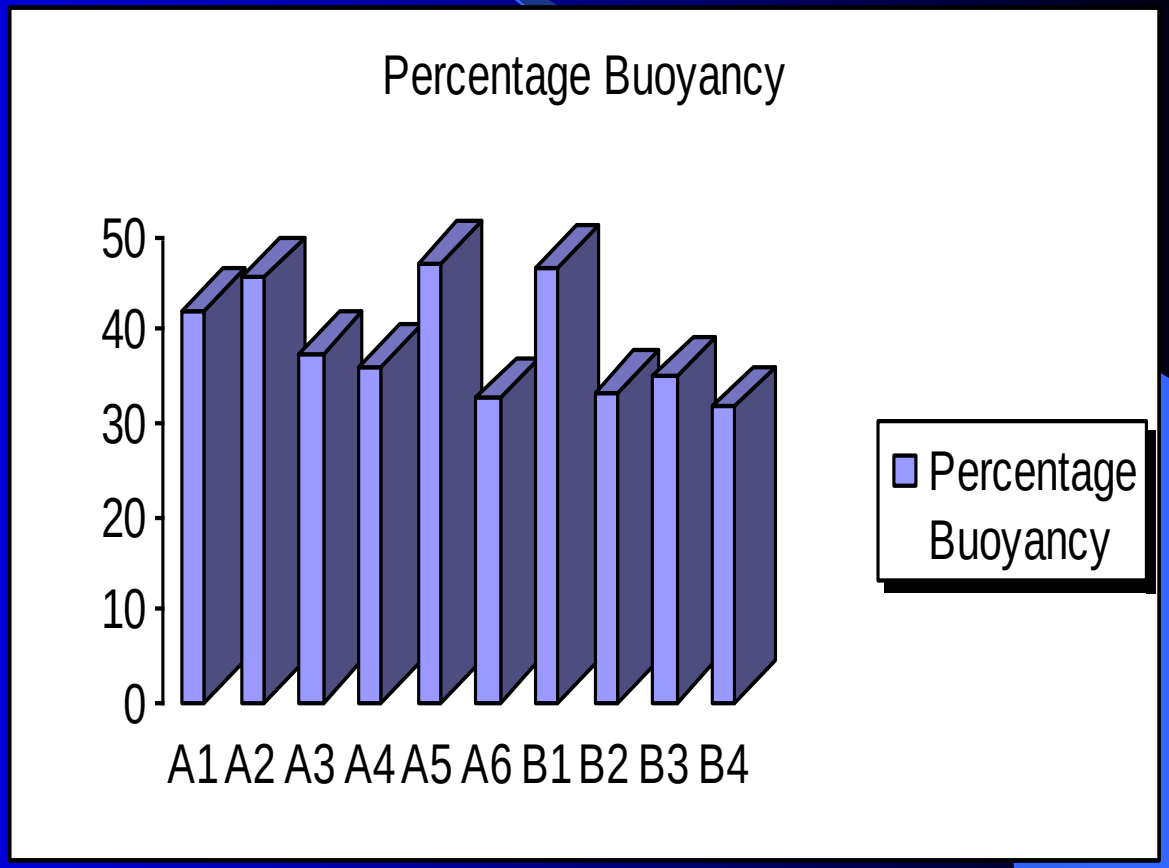
- Particle size
- Tapped density
- Angle of Repose
- Characterization of hollow ness
- Buoyancy or Floatability
- Percentage yield

Observation and result of micromeritics

Parameters-→ *Batches* | V	Average particle size(μm)	Tapped density (g/cm^3)	Bulk density (g/cm^3)	% Compressibility Index	Hausner ratio	Angle of repose (θ)
A1	237.2 ± 3.3	0.184	0.863	15.2	0.213	54 °19’
A2	258.0 ± 6.7	0.183	0.851	12.5	0.215	56 ° 12’
A3	273.5 ± 9.6	0.185	0.849	13.1	0.217	59 ° 23
A4	309.5 ± 2.2	0.179	0.746	15.8	0.239	36 ° 71’
A5	340.7 ± 5.9	0.175	0.734	10.2	0.238	31 ° 82’
A6	387.0 ± 9.8	0.158	0.725	9.6	0.217	29 ° 56’
B1	219.0 ± 2.7	0.164	0.910	12.6	0.180	32 ° 78’
B2	242.0 ± 3.6	0.175	0.967	13.7	0.181	34 ° 32’
B3	205.1 ± 8.1	0.172	0.987	15.9	0.174	31 ° 45’
B4	213.4 ± 7.2	0.160	0.984	12.6	0.162	25 ° 76’

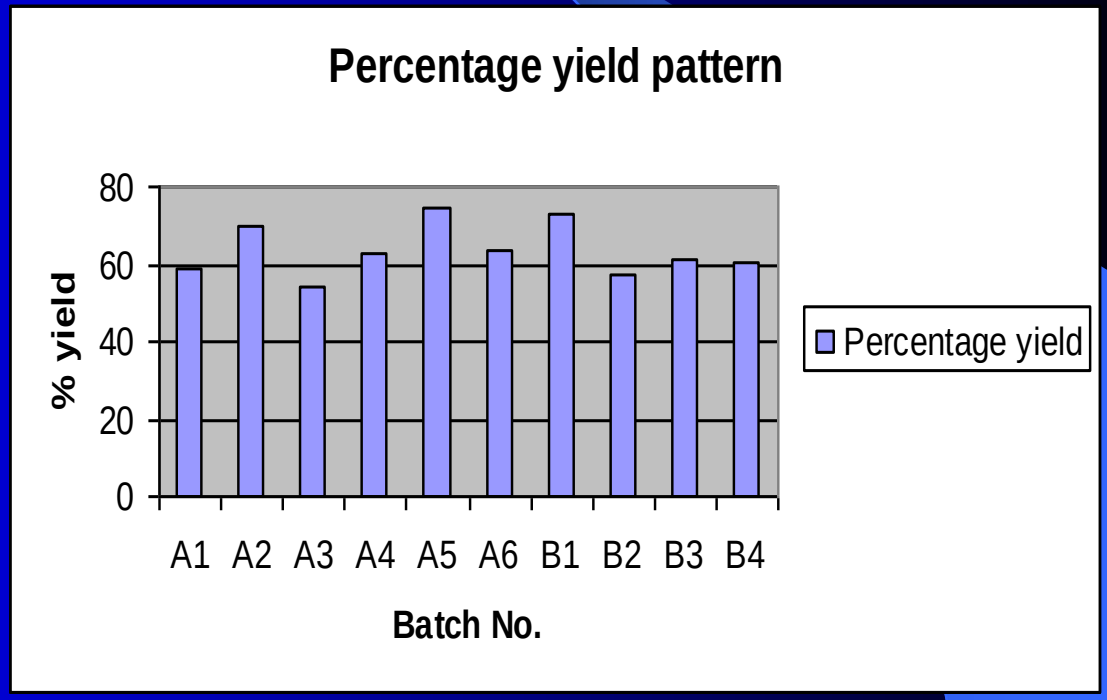
BUOYANCY

Batch No	Percentage Buoyancy
A1	42.2
A2	45.6
A3	37.5
A4	36.15
A5	47.15
A6	32.69
B1	46.65
B2	33.25
B3	34.89
B4	31.69



PERCENTAGE YIELD

Batch no.	Percentage yield
A1	58.86
A2	69.56
A3	54.45
A4	62.45
A5	74.42
A6	63.45
B1	73.25
B2	57.14
B3	61.54
B4	60.35



Analytical method

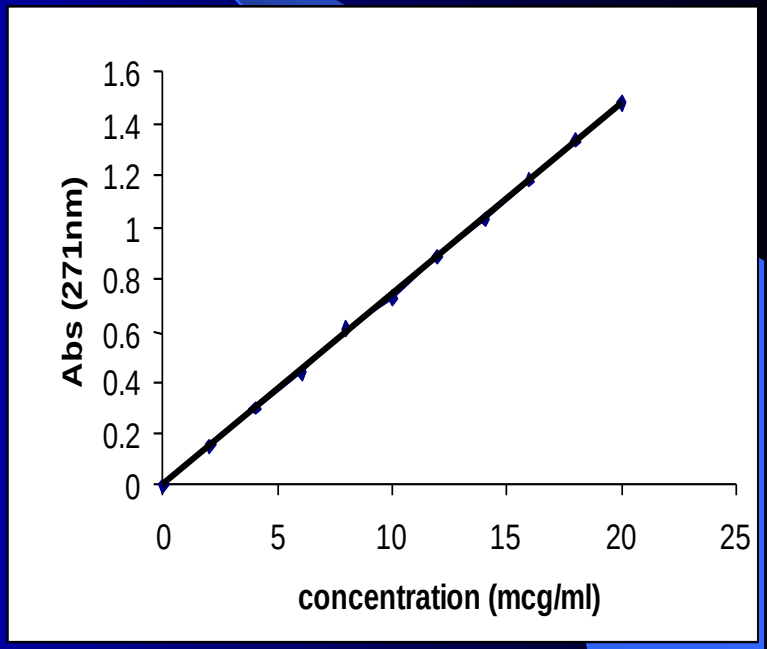
- Standard curve preparation
- Dissolution or drug release studies
- Drug loading or incorporation study
- Model fitting
- Stability Studies

Standard curve

S. No	Concentration (µg/ml)	Mean absorbance at 271 nm (±S.D.)	Regressed value
1	2	0.152 (±0.0031)	0.152
2	4	0.299 (±0.0014)	0.299
3	6	0.455 (±0.0025)	0.446
4	8	0.604 (±0.0079)	0.593
5	10	0.725 (±0.0020)	0.740
6	12	0.883 (±0.0019)	0.887
7	14	1.013 (±0.0033)	1.034
8	16	1.181 (±0.0057)	1.181
9	18	1.335 (±0.0017)	1.328
10	20	1.482 (±0.0029)	1.475

Y= 0.0735x+0.0054

Correlation coeff.(R) = 0.9998

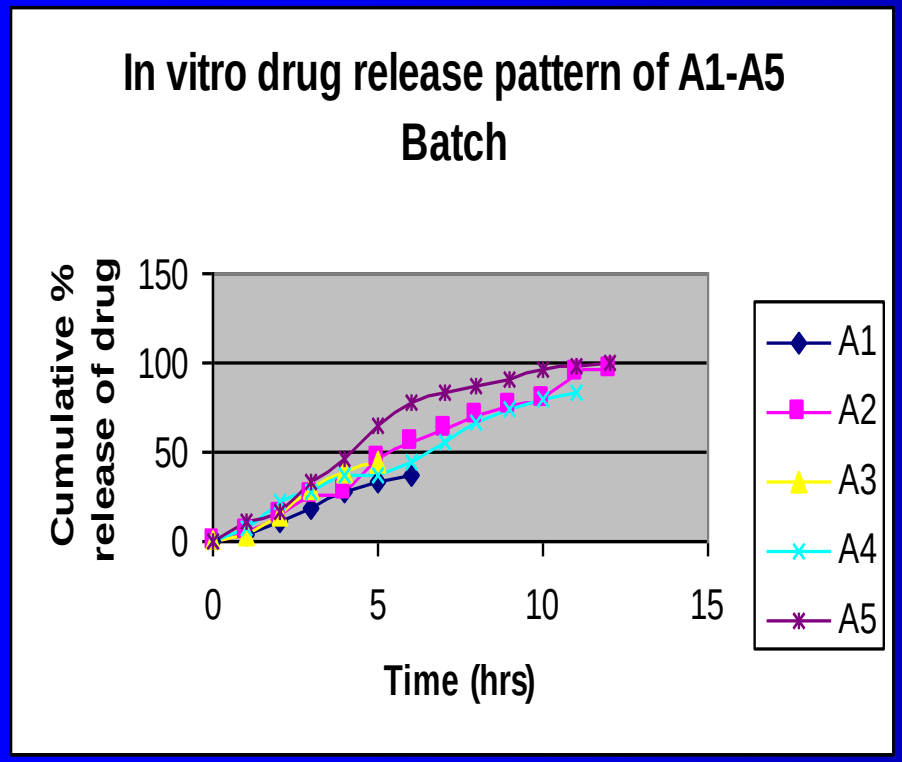


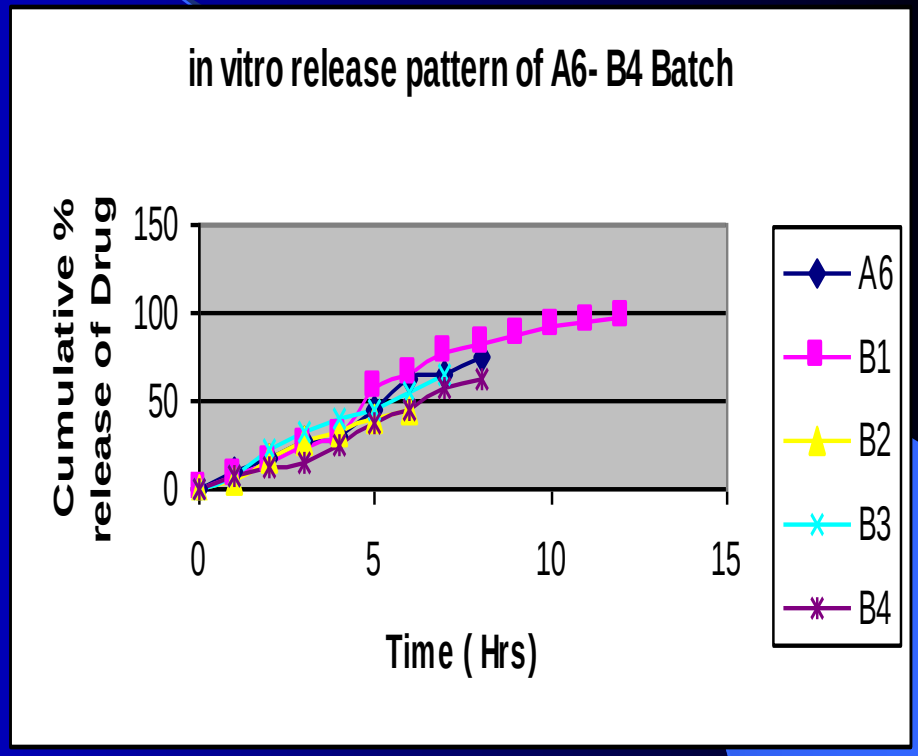
Calibration curve of THP in simulated gastric fluid pH 1.2

Dissolution study of microballoons

Time (hrs)	Cumulative RELEASE (%)									
	A1	*A2*	*A3*	*A4*	*A5*	*A6*	*B1*	*B2*	*B3*	*B4*
0	0	0	0	0	0	0	0	0	0	0
1	4.58	6.44	4.50	8.08	10.24	8.76	7.52	4.52	6.50	6.78
2	10.94	14.78	15.50	21.51	17.39	18.10	14.12	17.93	21.71	11.56
3	18.92	26.04	29.49	27.06	33.51	27.14	25.42	28.46	31.86	15.36
4	27.39	27.88	39.24	36.40	46.31	29.21	29.40	33.00	39.74	25.68
5	33.66	46.02	44.58	37.18	64.04	46.06	58.66	40.09	44.30	36.85
6	36.85	56.48	--	44.04	78.23	61.58	65.79	45.57	54.65	45.56
7	--	62.62	--	55.45	82.53	66.01	77.26	--	65.55	56.85
8	--	71.22	--	66.01	86.38	74.22	82.28	--	--	62.85
9	--	75.75	--	74.22	90.01	--	86.89	--	--	--
10	--	80.05	--	79.84	96.32	--	92.50	--	--	--
11	--	94.50	--	82.41	98.95	--	94.80	--	--	--
12	--	96.95	--	--	99.25	--	97.32	--	--	--

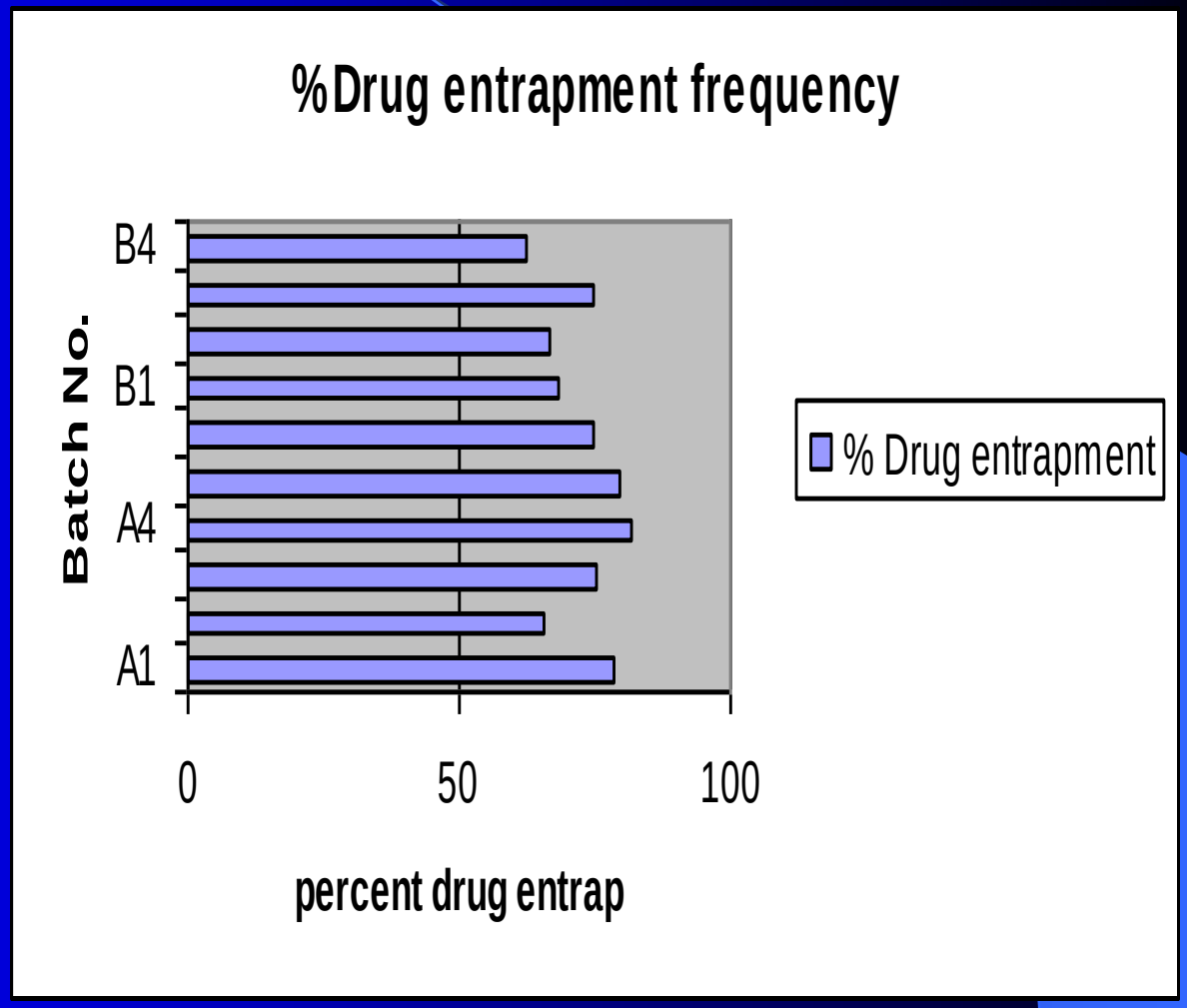
Graphs of comparative studies on drug release



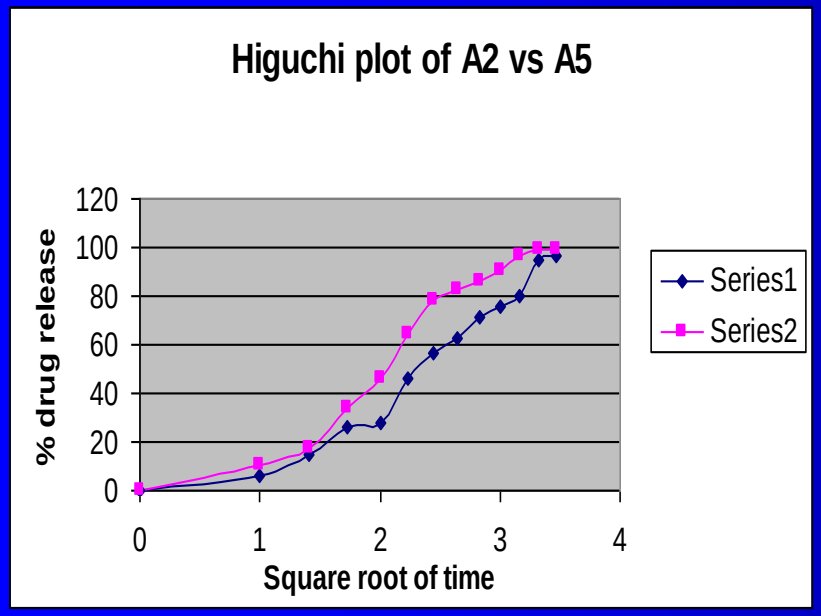


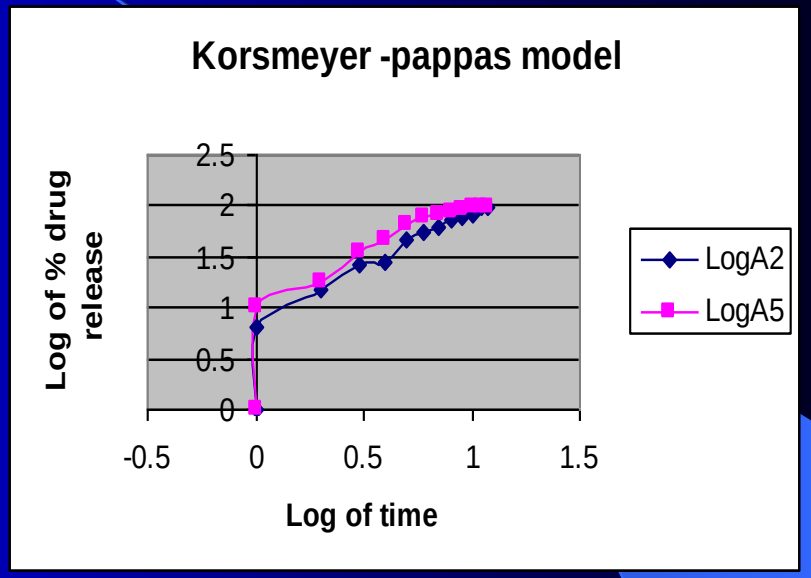
DRUG LOADING In Microballoons

Batch no	% Drug entrapment
A1	78.55
A2	65.46
A3	75.2
A4	81.5
A5	79.65
A6	74.6
B1	68.4
B2	66.9
B3	74.68
B4	62.15



Model Fitting studies on drug release for optimized batch A2 and A5





Stability Studies of optimized Floating microsphere

I. Accelerated stability studies according to WHO for shelf life determination

Temp °C	Slope x10^{-4}	K x10^{-4} (day^{-1})	Log K	Absolute Temp (°K)	1/T x10^{3}	Shelf life at 25°C
40	-0.4666	1.073	0.0305	313	3.194888	1.59 year
50	-0.1666	0.382	-0.4179	323	3.095975	
60	-0.1000	0.2303	-0.637	333	3.003003	
25	-.029	0.0667	-1.175	298	3.355704	

Table 1: Calculation for shelf life

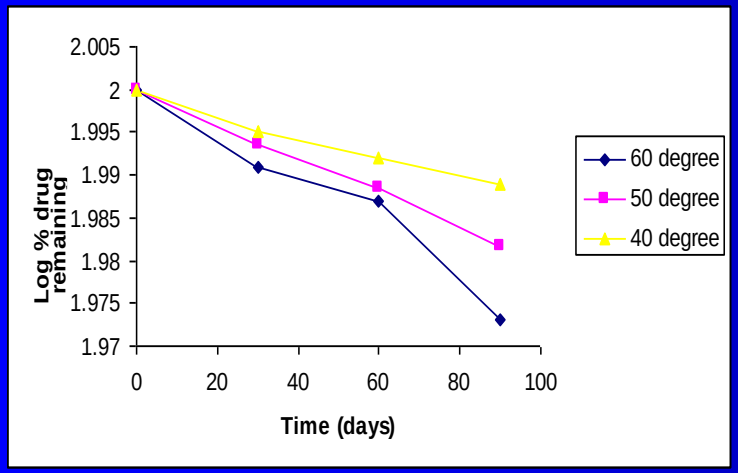


Fig. 1: Kinetics of drug degradation in optimized multiparticulate formulation(A5)

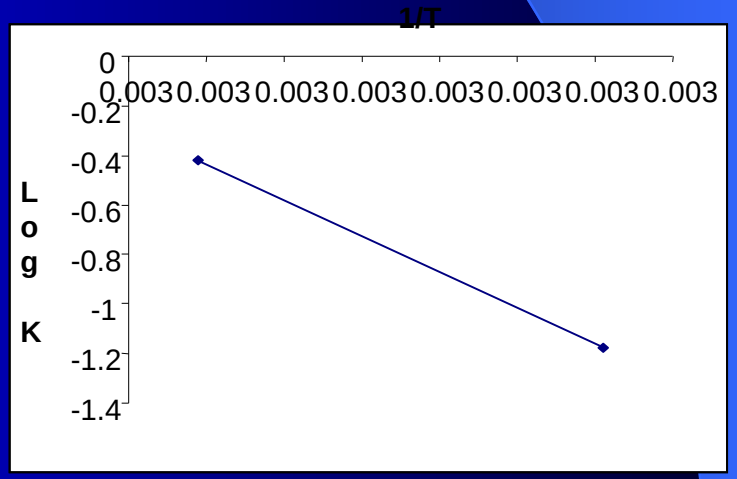


Fig. 2 :Arrhenius plot for optimized multiple unit formulation

II. Accelerated stability studies according to ICH guidelines

Time (days)	Mean area value	Concentration (µg/ml)	Drug content (mg)	% Drug remaining	Log % drug remaining
0	562749	7.684	38.42	100	2
30	560407	7.650	38.26	99.58	1.9981
60	552794	7.600	38.00	98.90	1.9922
90	547963	7.568	37.84	98.47	1.9884

Table 2: Degradation of Theophylline in formulation A5 at 40±0.5°C and 75% RH

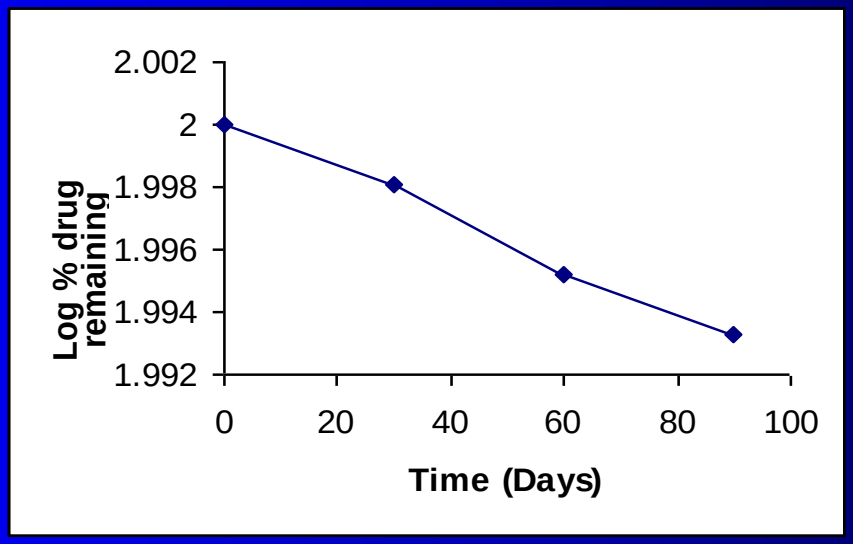
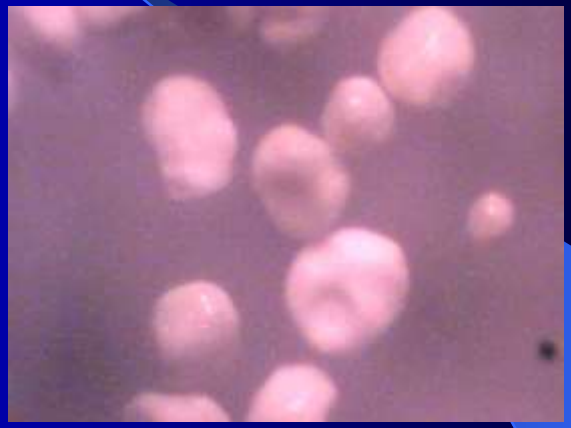


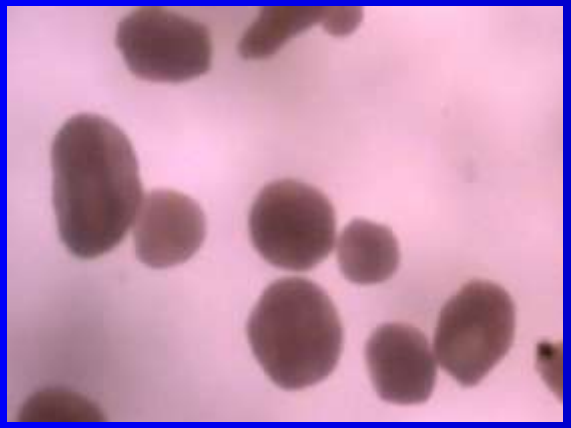
Fig 2: Degradation kinetics of Theophylline in optimized multiparticulate formulation (A5) at 40±0.5°C and 75% RH

Advance studies

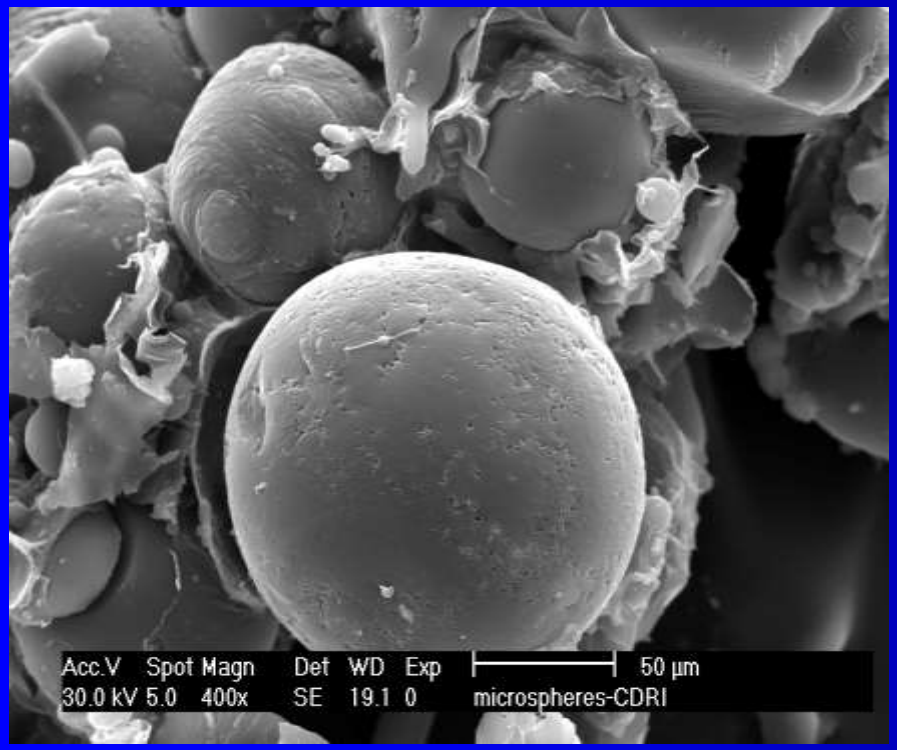
- Photomicrographs
- Scanning Electron Microscopy
- F T –Infra Red Spectroscopy
- Differential Scanning Calorimetry
- GC

PHOTOMICROGRAPHS



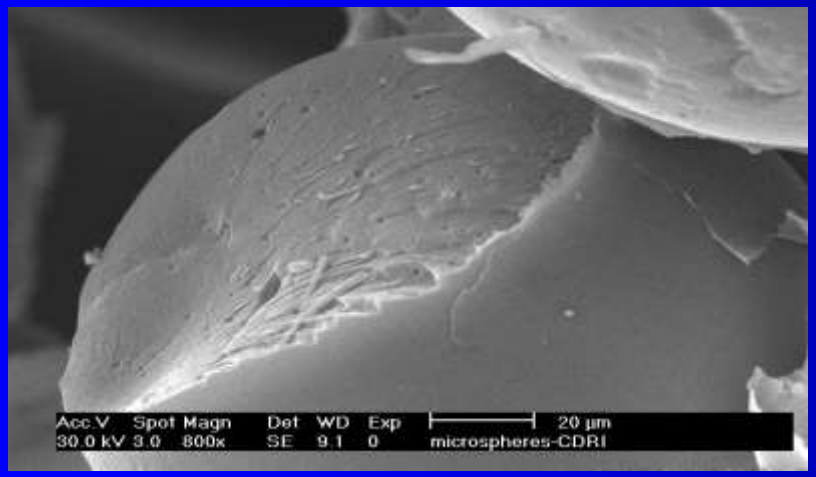


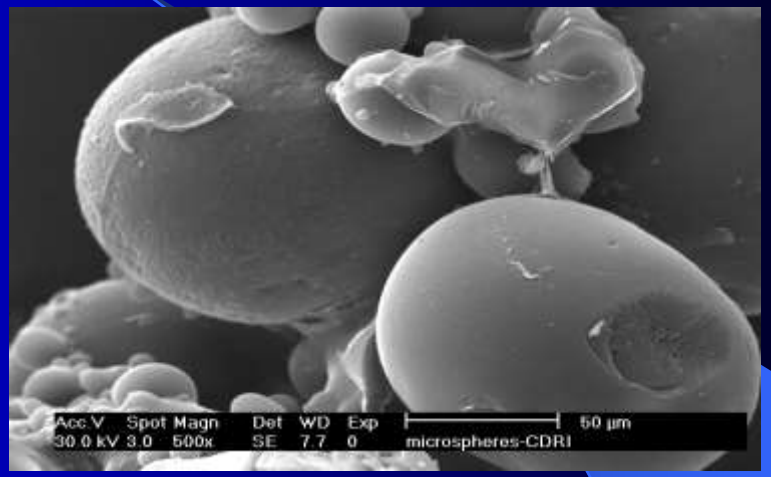
Scanning Electron Microscopy

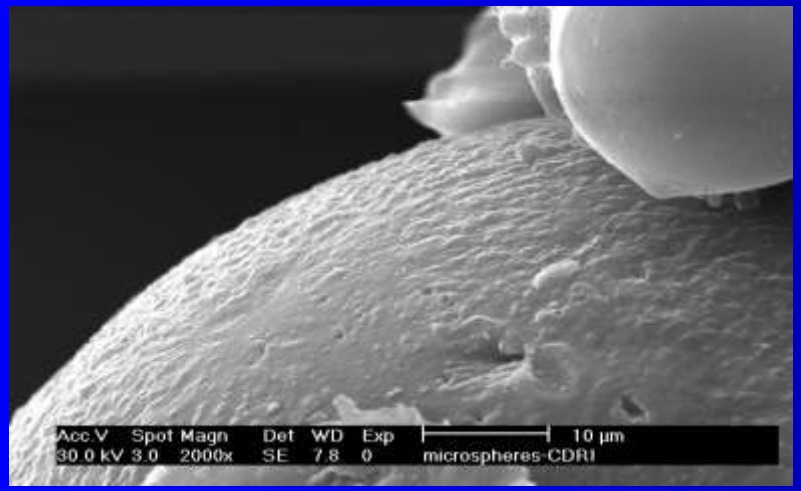


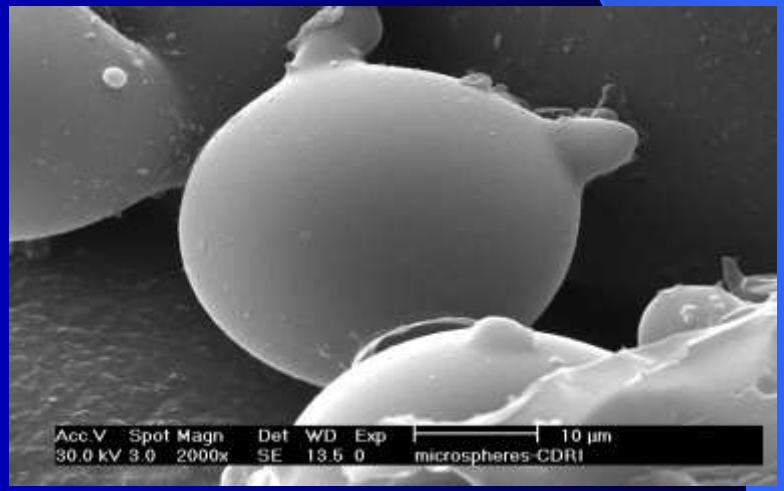
- Certain pores are also visible which denotes porosity.
- Surface Topography shows smooth texture.

SEM Pictures

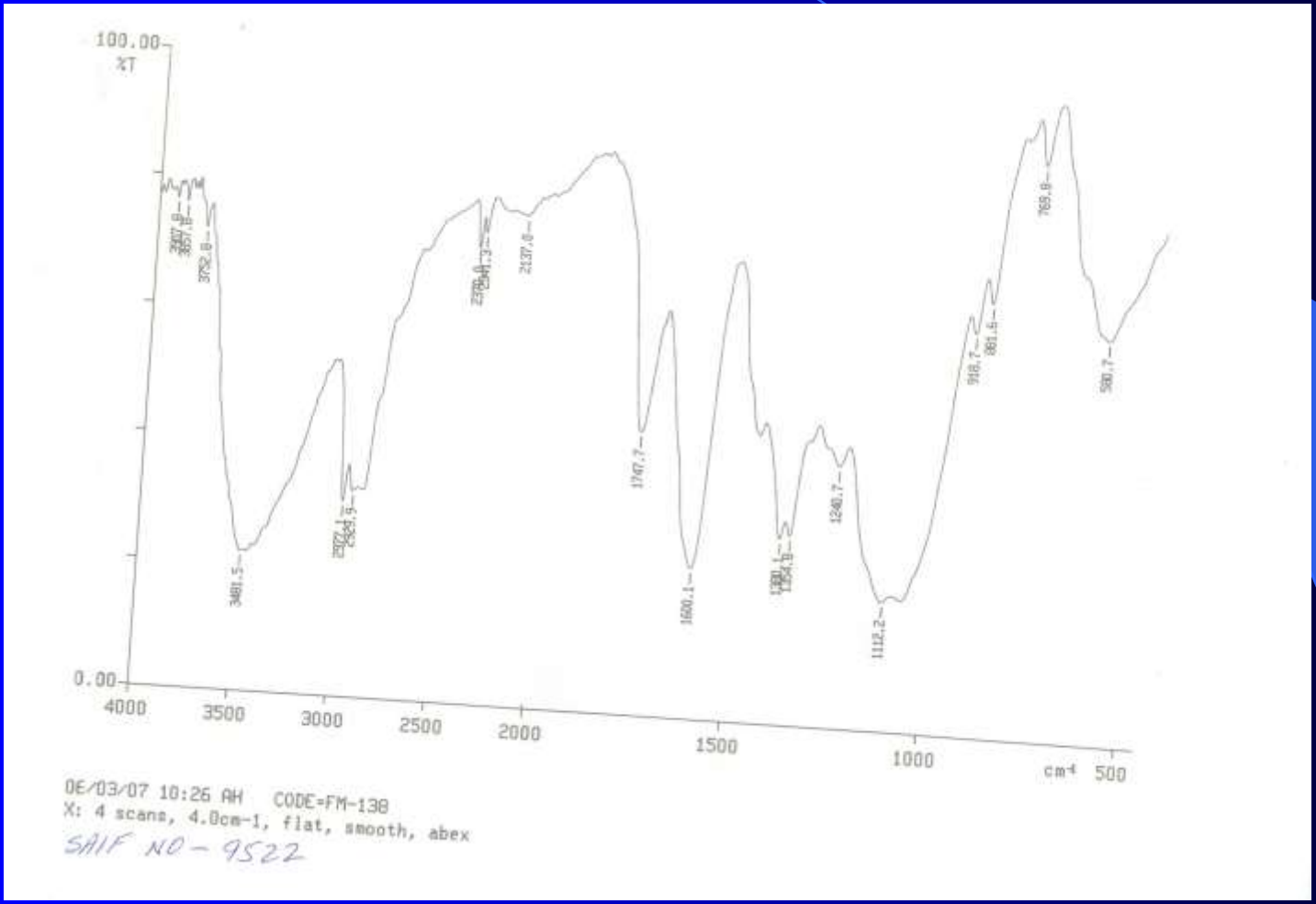








FT IR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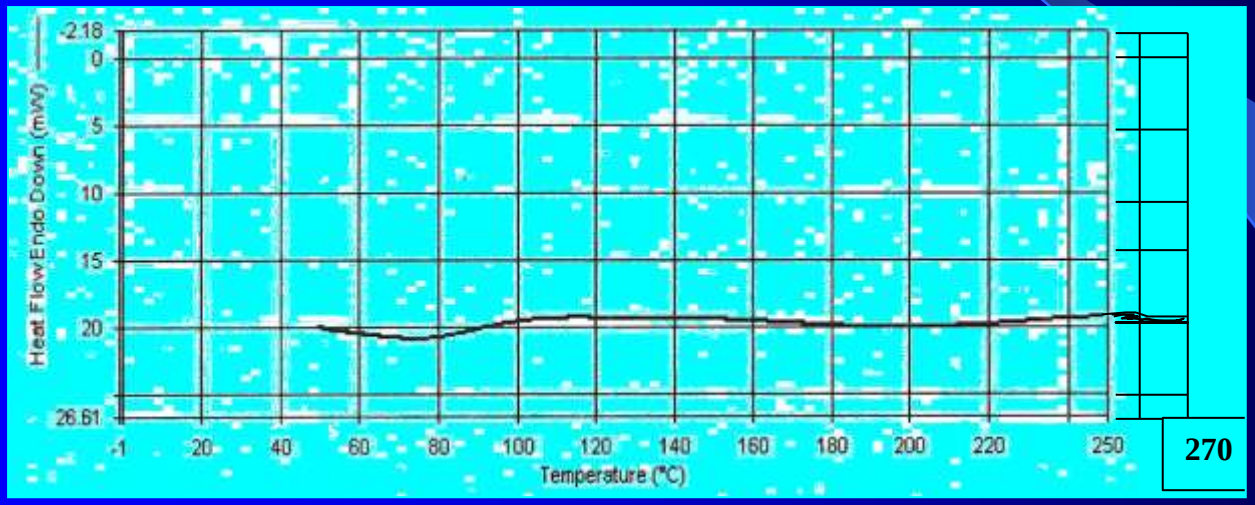
DSC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15
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26.61
Heat Flow Endo Down (mW)
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40
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100
120
140
160
180
200
220
250
Temperature (°C)
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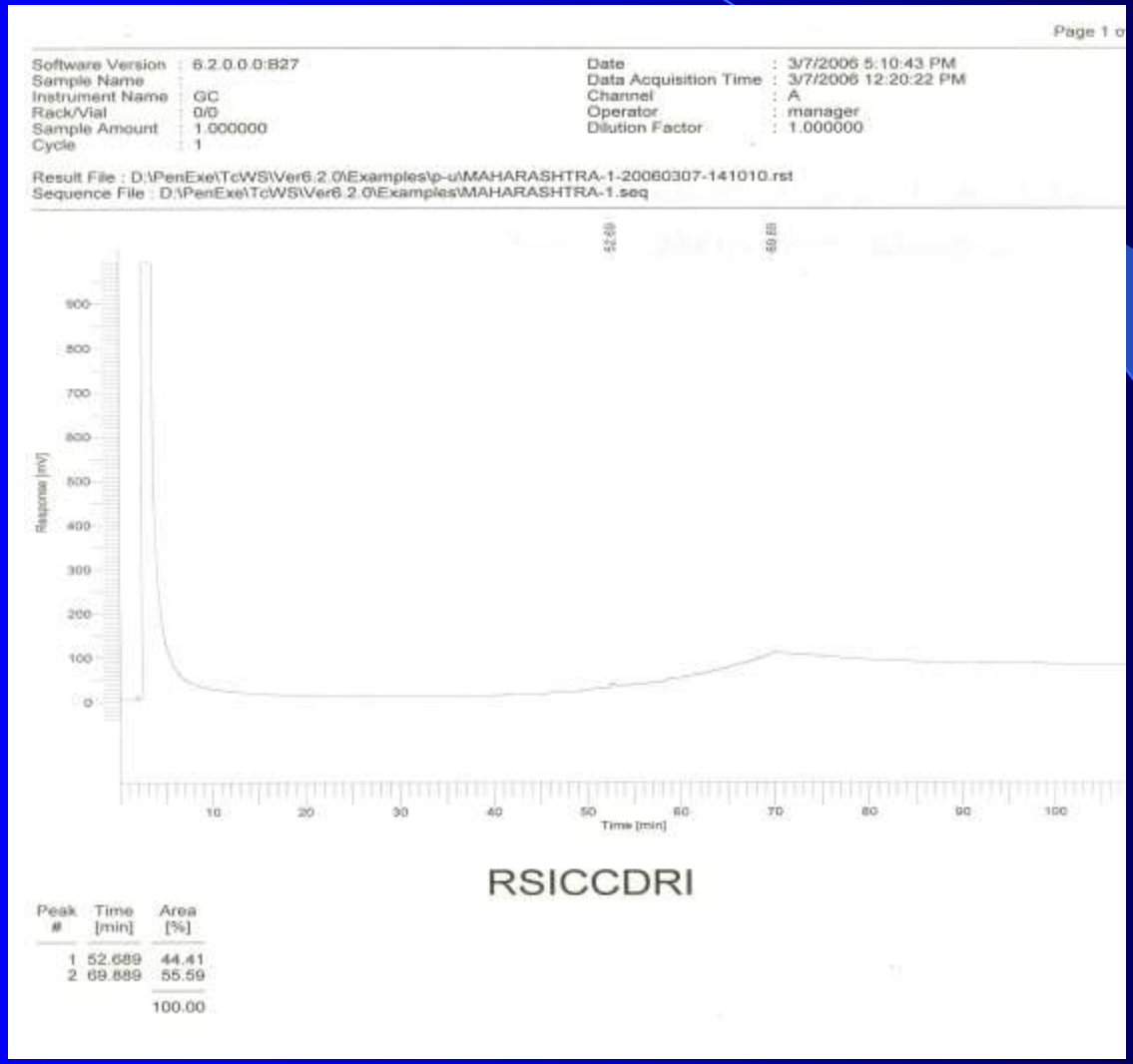
Gas Chromatography



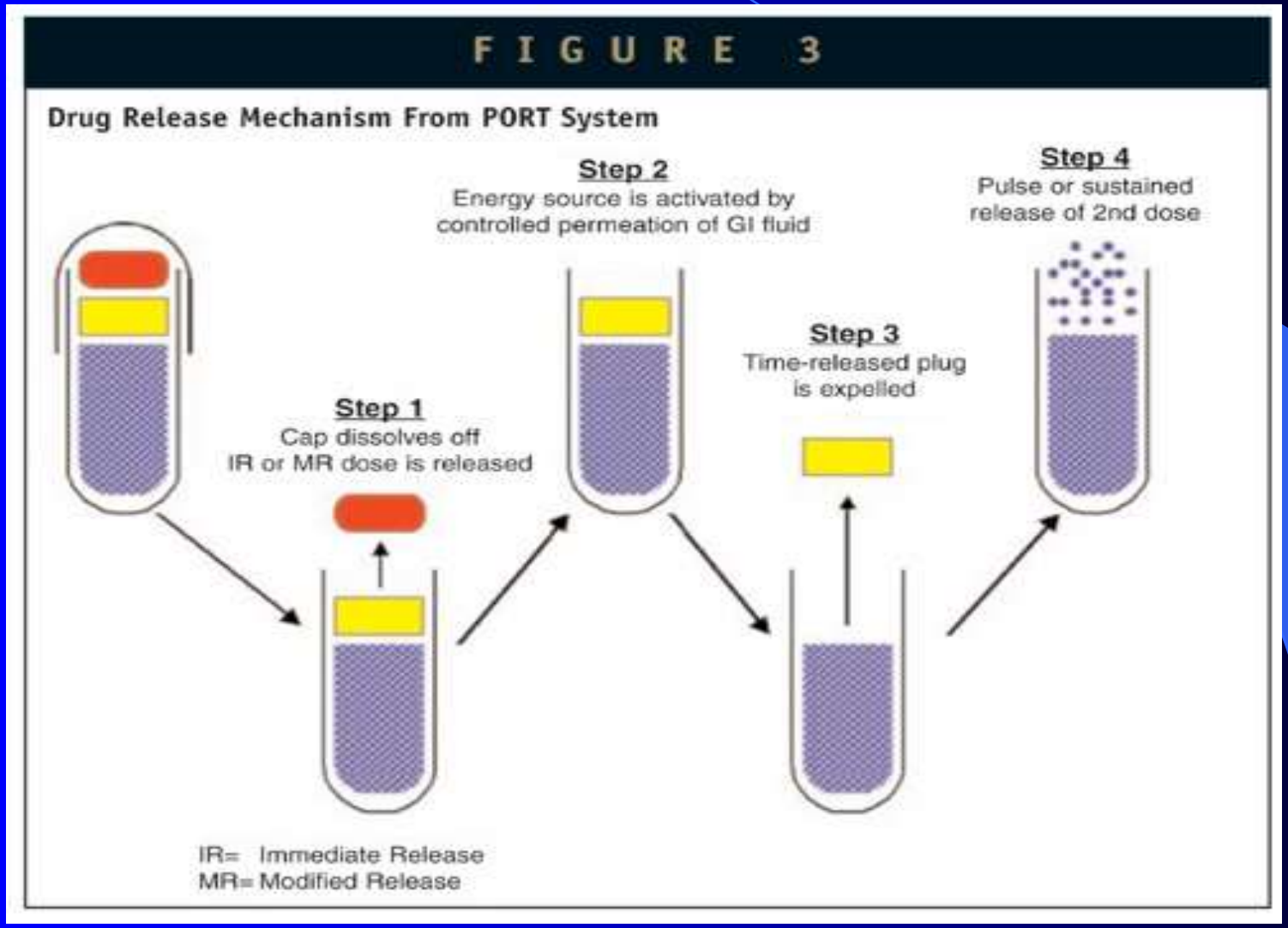
PREPARATION OF DOSAGE FORM

Formulation of Capsule:

Batches of Micro-balloons	% Yield Micro-balloons	Micro-balloons Wt. (mg)	Drug entrap i.e Dose (mg)	Lactose (Diluent) (mg)	Total wt. Of HBS Capsule (Microballoons + Lactose) mg
A1 a	58.86	588.6	196.25	411.4	1000
A2 a	69.56	695.6	163.50	304.4	1000
A3 a	54.45	544.5	188.00	455.5	1000
A4 a	62.45	624.5	203.75	375.5	1000
A5 a	74.42	744.2	199.13	255.8	1000
A6 a	63.45	634.5	186.50	365.5	1000
B1 b	73.25	732.5	171.00	267.5	1000
B2 b	57.14	571.4	167.25	428.6	1000
B3 b	61.54	615.4	186.70	384.6	1000
B4 b	60.35	603.5	155.38	396.5	1000

Preparation of dosage form

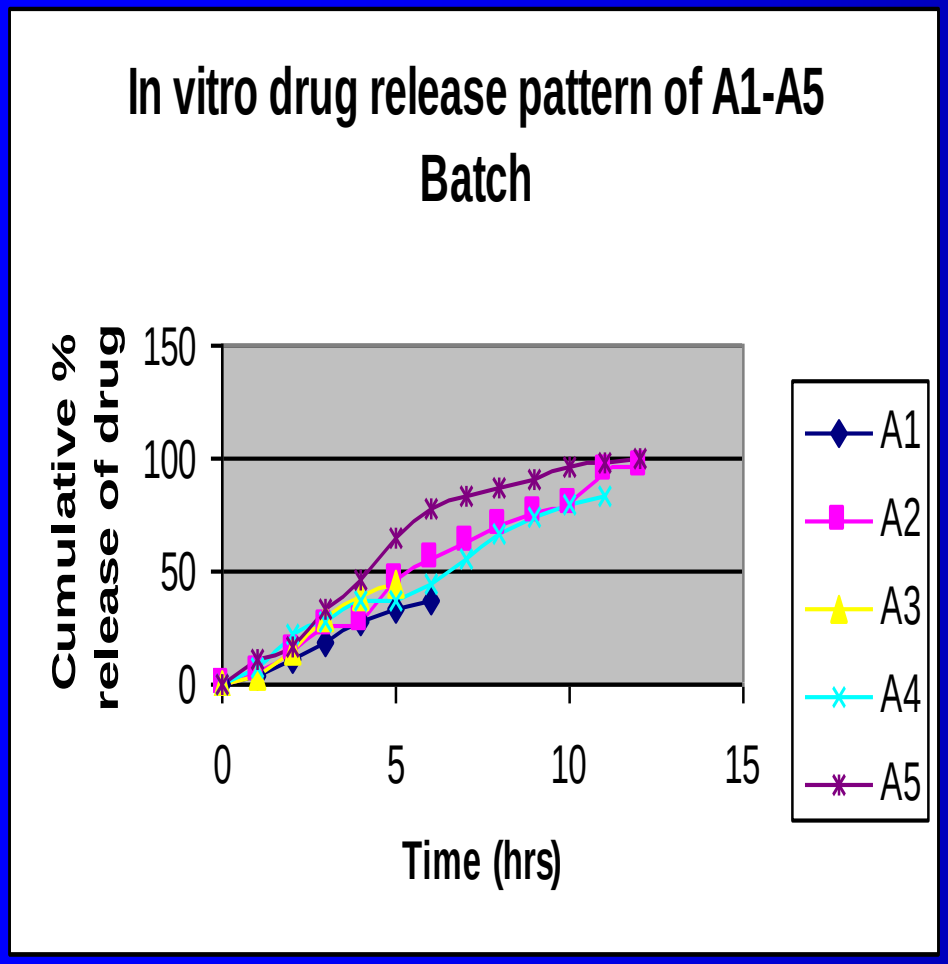
- Drug release mechanism of Capsule

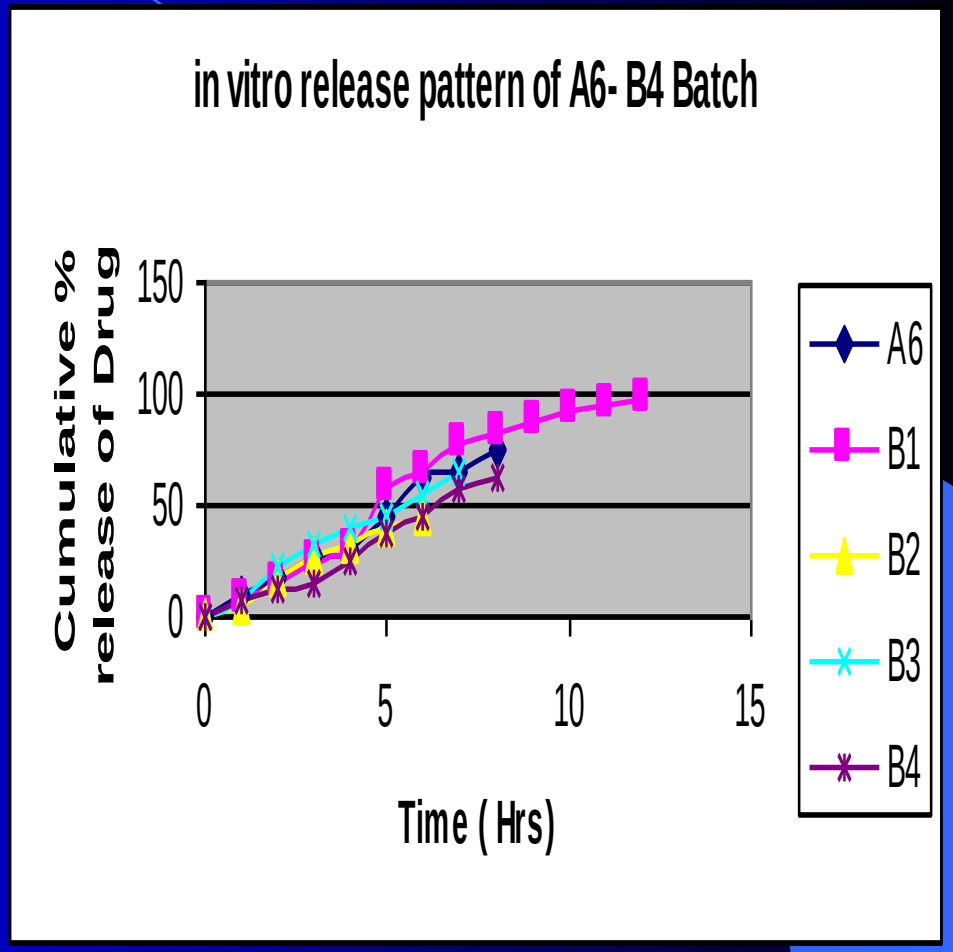


Dissolution studies for HBS Capsule dosage form

Time (hrs)	Cumulative RELEASE (%)									
	A1	*A2*	*A3*	*A4*	*A5*	*A6*	*B1*	*B2*	*B3*	*B4*
0	0	0	0	0	0	0	0	0	0	0
1	6.58	8.44	8.50	8.08	10.24	8.76	7.52	9.52	10.50	7.78
2	11.94	14.78	15.50	21.51	17.39	18.10	14.12	17.93	21.71	11.56
3	18.92	26.04	29.49	27.06	33.51	27.14	25.42	28.46	31.86	15.36
4	27.39	27.88	39.24	36.40	46.31	29.21	29.40	33.00	39.74	25.68
5	33.66	46.02	44.58	37.18	64.04	46.06	58.66	40.09	44.30	36.85
6	36.85	56.48	--	44.04	78.23	61.58	65.79	45.57	54.65	45.56
7	--	62.62	--	55.45	82.53	66.01	77.26	--	65.55	56.85
8	--	71.22	--	66.01	86.38	74.22	82.28	--	--	62.85
9	--	75.75	--	74.22	90.01	--	86.89	--	--	--
10	--	80.05	--	79.84	96.32	--	92.50	--	--	--
11	--	94.50	--	82.41	98.95	--	94.80	--	--	--
12	--	95.95	--	--	99.02	--	96..32	--	--	--

Comparative studies of drug release from HBS Capsule



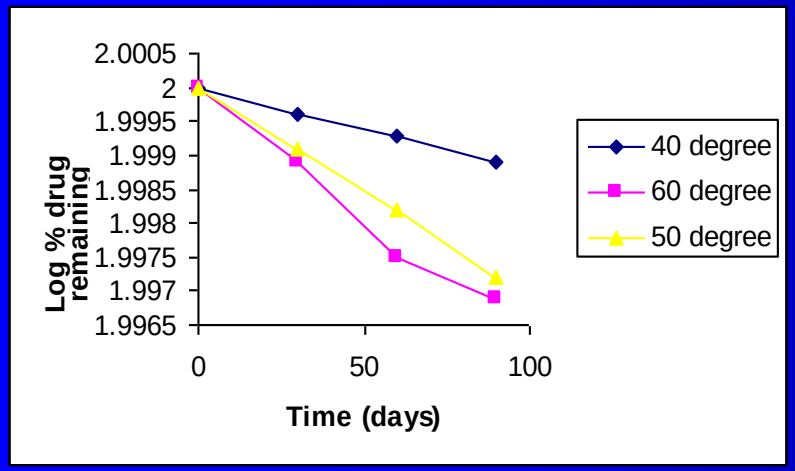


Stability Stability Studies of optimized HBS Capsule

Accelerated stability studies according to WHO for shelf life determination

Temp (^{0}C)	Slopex10^{-4}	K (day^{-1}) x10^{-4}	Log K	Absolute Temp (^{0}C)	1/Tx10^3	Shelf life at 25°C
40	-0.1333	0.3069	-0.5130	313	3.19488	1.9 year
50	-0.2666	0.6139	-0.2119	323	3.09597	
60	-0.4666	1.0745	0.0312	333	3.00300	
25	-0.024	0.0552	-1.2574	298	3.35570	

Table 1: Calculation of shelf life



15/06/22

Fig 1: Kinetics of drug degradation from optimized HBS capsule

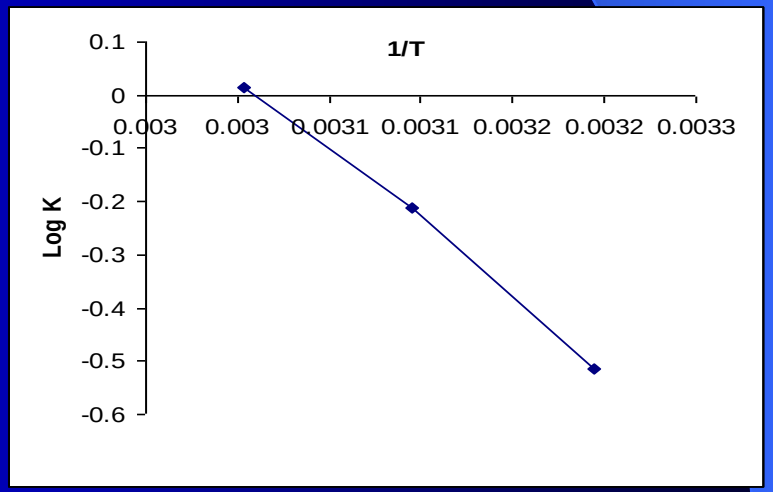


Fig. 2: Arrhenius plot for optimized capsule

Accelerated stability studies according to ICH guidelines

Time (days)	Mean area value	Concentration (µg/ml)	Drug content (mg)	% Drug remaining	Log % drug remaining
0	292667	39.978	199.89	100	2
30	292022	39.892	199.46	99.78	1.9990
60	291510	39.824	199.10	99.60	1.9982
90	290604	39.700	198.38	99.24	1.9966

Table 2: Degradation of Theophylline in formulation A 2 at 40°C ±0.5°C and 75% R.H.

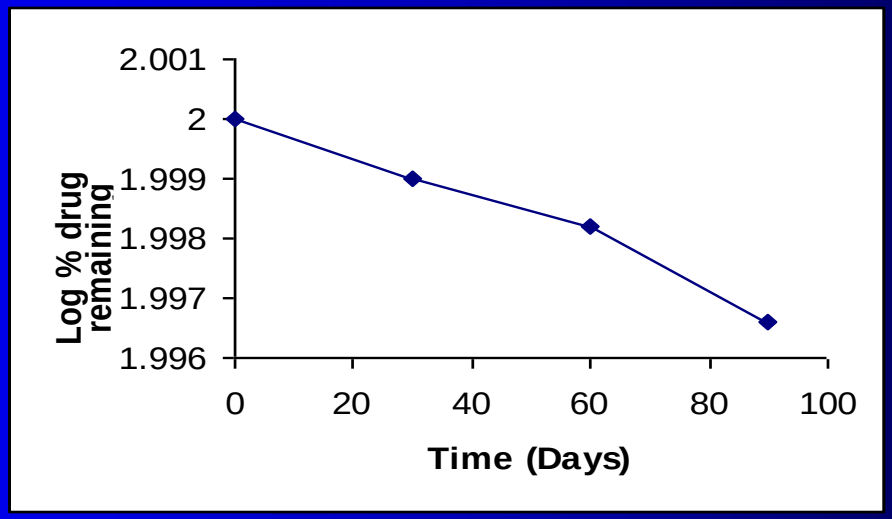


Fig 3: Degradation kinetics of Theophylline in optimized formulation

SUMMARY AND CONCLUSION

Following conclusion can be drawn from the results obtained:

1. Gastroretentive formulations in the form of HBS capsule and floating microspheres was developed.
2. HBS capsule A5 Batch was found to be satisfactory in terms of drug release , floatability and drug entrapment and could be used as an alternative to conventional dosage forms.
3. *In vitro* drug release could be obtained for up to 12 hours using Gastroretentive HBS capsule.
4. A maximum *in vitro* drug release of 99.02% in 12 hours for Gastroretentive HBS capsule was obtained for A5 batch.
5. Floatation was achieved for the entire study period.
6. Shelf life 1.9 years was assigned to optimized single unit formulation.
7. Shelf life 1.59 years was assigned to optimized multiple unit formulation.
8. Accelerated stability studies were carried as per WHO and ICH guidelines. The formulation was found to be stable and exhibited minimal degradation.

FUTURE SCOPE

- To Study size reduction parameter i.e an approach towards nano technology.
- The most targetted oriented release of drug in the cure of disease related to stomach.
- To study various dosage forms formulated via use of microballons.
- To study effect solvent composition on drug release.
- To study effect of stirring rate during microsphere preparation on drug release.

THANK YOU

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