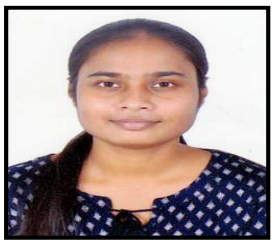
Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

https://doi.org/10.36673/AJRCPS.2020.v08.i03.A34



PREPARATION OF SUSTAIN RELEASE MICROSPHERES OF CYCLOBENZAPRINE HYDROCHLORIDE USING VARIOUS POLYMERS

Shweta Singh Gautam*[1], Jai Narayan Mishra[1], Navneet Kumar Verma[2]

[1*]Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur, Uttar Pradesh, India.

[2]Buddha Institute of Pharmacy, GIDA, Gorakhpur, Uttar Pradesh, India.

ABSTRACT

Cyclobenzaprine coordination compound could be a midway acting relaxant, synthetically like amitriptyline coordination compound with higher action. The correct part of activity of muscle relaxant coordination compound that is not to be determined. Be that because it might, it basically acts at the mind stem to decrease tonic physical engine movement, impacting each gamma and alpha engine neurons. Cyclobenzaprine coordination compound could be a white, crystalline antidepressant alkane series salt with the data-based formula $C_{20}H_{21}N\_HCl$ and a sub-atomic load of 311.9. It's a liquefying purpose of 217ºC, and a pKa of eight. 47 at 25ºC. It is soluble in water and alcohol freely, meagerly soluble in alcohol, and insoluble in various kinds of solvents of hydrocarbon. If liquid solutions square measure created base-forming, the free base separates. Sustained unharness microspheres of muscle relaxant complex, a striated muscle relaxant that relieves muscle spasm of native origin while not busy with muscle. Muscle relaxant complex is extremely water soluble drug, having low oral bioavailability (33-55%) thanks to in depth metabolism of drug. And also the indefinite quantity forms on the market in market were having trice daily administration. The most objective of gift study was developed to boost oral bioavailability, scale back the frequency of drug administration, and improve patient compliance. During this study, sustained unharness microspheres of muscle relaxant complex was ready by solvent evaporation techniques exploitation Eudragit (EU) RS one hundred, Chitosan and Na alginate as polymers and yield, particle size, encapsulation efficiencies and *in vitro* unharness of the ready microspheres were evaluated. The results showed that proportion yield, encapsulation efficiencies and particle size were influenced primarily by chemical compound concentration, style of chemical compound and stirring speed. Results of the *in vitro* study shows that the required rate is achieved by up to twelve hrs. DSC results showing there's no interaction between drug and polymers. SEM results of optimized microspheres showing distinct, spherical microspheres.

KEYWORDS

EU (eudragit RS-100), Chitosan, Sodium alginate, Skeletal muscle relaxants, Sustain release, DSC and SEM.

Author for Correspondence:
Shweta Singh Gautam,
Kailash Institute of Pharmacy and Management,
GIDA, Gorakhpur, Uttar Pradesh, India.

Email: shweta.rockss78@gmail.com

INTRODUCTON

Two conditions would be required for oral medication delivery. Initially, time of activity ought to be single, regardless of whether it be for a few days or a little while, similarly as with or for the lifetime of the patient, as in hypertension or diabetes. Second, it ought to disseminate the

straight to the spot of activity subsequently limiting or taking out side effects. This may require circulation to downright receptor, or to confined to or to all out regions of the body. In the previous decade extraordinary intrigue got inciting on supplanting customary organization of medication by novel appropriation framework which would give up adequate sums which are get from a divider which supplies at control rate from a more drawn out time. In a perfect world a give substance having impact upon the faculties to make yare wanted restorative acting ought to get to quickly at the spot of acting in lively sum, continue being there for wanted time, let free different locales and get limited from the place. The captivating aftereffect of pharmaceutical research is the way that assimilation rate of the medication can be decremented by diminishing its rate of surrender from the dose structure. The item as intended for continue activity, support discharge, postponed action[1].

Sustain release

Pharmaceutical items put plainly for fundamental method for utilizing by the oral method for the legislature not assessing the most continuous number of things taken round to (straight away, experienced or controlled give out) and the plan of the sum frames (either strong or fluid), must be got more prominent, more grounded, progressively complete inside the characteristics of GI physiology, pharmacokinetics pharmacodynamics and principles to make configuration is most critical to complete a foundational move close to the with a decent result improvement of a by oral pharmaceutical sum form[1]. Following focal points of coordinating a single bit of a drug that is released over a comprehensive time span, instead of number of measurements, have been clear. The longing to keep up an adjacent unwavering or uniform blood estimation of a medication reliably unwinds into better quiet consistence, and in like manner overhauled clinical sufficiency of the solution for its proposed use[2]. In view of expanded disorder and cost engaged with showing of new medication segments, has concentrated logically basic idea on progress of continued discharge or medication conveyance systems[3]. Framework structure is ordinarily utilized for the reason behind supported discharge. To be perfectly honest, a cross segment is portrayed as blend of no short of what one medications with gelling ace for example hydrophilic polymers[4]. This is the release system which controls and hauls out the landing of the medicine which is separated or dispersed. Eventual outcomes of pharmaceutical research portray that osmosis rate of a drug can be decreased by diminishing its rate of release from the portion outline. The thing so point by point are appointed as proceeded with action, upheld release, deferred movement, postponed action, station, respiratory, obstructed release and composed release medication[5,6]. Over the past thirty years, because the expense and disarray connected with advancing new entity have extended with related to affirmation of the medical specialty nice conditions, strengthened discharge advancement is new has been ordinarily made and has created completely different revelations. The basic purpose is to verify a relentless state blood level that's medicinally non-savage and viable for a good stretch of your time. For composition a reputable bit form it's an elementary half to attain this objective. Upheld unharness, bolstered action, delayed movement, controlled unharness, enlarged action square measure term used for drugs transport structure that square measure planned to attain delayed therapeutic impact by endless emotional answer for a broad stretch of your time once association of a lone section. By virtue of oral proceeded with free estimation form, an impact is for one or two of hours betting on living course of action time of definition within the rat. Traditional half treatment needed an irregular little bit of accommodating consultants. These consultants square measure purpose by purpose for the age of most outstanding soundness, activity and bioavailability. There for most of prescriptions, conventional techniques for drug association are feasible, anyway a couple of meds harmful and have thin helpful degrees. Scarcely any meds moreover have dissolvability issues.

MATERIAL AND METHODS

Pre-formulation Studies[7]

Pre-formulation contemplates are the initial phase in the justification advancement of dose types of a medication.

The objectives of Pre-formulation thinks about are:

- To set up the vital physicochemical qualities of another medication substances.
- To decide its dynamic discharge rate profile.
- To build up its similarity with various excipients.

Ultra-Violet Spectroscopy

Before arrangement of continued discharge microspheres of cyclobenzaprine hydrochloride, standard twist of cyclobenzaprine hydrochloride in different media was gained to quantify the precedents. All plans were recently orchestrated before use[8].

Phosphate Buffer of 7.4 pH Preparation

In 0.2 M KH_2PO_4 put 250ml in 1000ml volumetric container and 195.5ml of 0.2M sodium hydroxide will be added to it. Volume was made with water and pH was changed till 7.4.

Preparations of 0.1N HCl

Conc. HCL Pipette out 8.5ml of into a volumetric glass and make up volume with water. pH was kept up.

CBz Standard solution preparation

Stock solution - I

A 100mg of CBz weighted and put in volumetric cup. Making the up the volume utilizing water to give 1000mcg/ml arrangement.

Stock solution -II

From I stock solution take 10ml and place in a 100ml volumetric flask and diluted with water to 100ml to get 100mcg/ml.

Stock solution-III

From stock solution -II, a 10ml of aliquote was made up to 100ml to get 10mcg/ml.

Similar dilutions were prepared from stock solution-I in different media like 0.1N HCl, and pH 7.4 buffer solutions.

Determination about absorption maxima (λmax) for CBz hydrochloride

A 10mcg/ml standard solution of CBz hydrochloride on a double beam spectrophotometer against respective media blanks.

An absorption maximum (λmax) of 290nm was gained for all solutions and was selected to preparation standard curve[9].

Standard curve preparation

Standard bends of cyclobenzaprine was acquired in 7.4 pH supports, 0.1N and water. Aliquotes of different arrangement of cyclobenzaprine hydrochloride standard arrangement of 100mcg/ml (stock arrangement II) was taken and weakened to get fixations from 5to 25mcg/ml with suitable media[8].

Preparation of Stock Solution in Distill water

Cyclobenzaprine hydrochloride were precisely gauged 100mg and exchanged to 100ml volumetric jar. Medication was disintegrated in 50ml of water shaken physically for 10 moment and volume was made up to the stamp with a similar dissolvable. This was the standard stock arrangement containing 1mg/ml (1000µg/ml). 1ml of this readied arrangement was pipette out and exchanged to the 10ml volumetric jar, and volume made up to 10ml with same dissolvable to acquired last fixation 0.1mg/ml (100µg/ml i.e. stock arrangement).

Spectrophotometric scanning of CBz hydrochloride in distill water

An appropriate portion of 1, 2, 3, 4 and 5ml of cyclobenzaprine hydrochloride stock arrangement in distil water was pipette out and exchanged to isolate 10 ml volumetric jar and afterward volume made up to 10ml with methanol to get focus 0.1, 0.2, 0.3, 0.4, 0.5µg/ml. The arrangements were checked independently between 200nm to 400nm. The spectrum of drug was recorded. Wavelength 290nm was selected for further study.

Preparation of Calibration Curve of CBz hydrochloride

Taken a series of concentration of ranging between 0.1-0.5µg/ml. Measure absorbance using spectrophotometer at 290nm against distill water as blank.

FTIR STUDY OF DRUG[10,11]

Infrared Spectrum of the medication test was acquired utilizing FTIR-8400S, Shimadzu spectrophotometer. One mg of the medication was blended with 100 mg of KBr in a mortar by trituration and the blend was packed into a pellet at 10ton/cm2in a pellet creator. Sample was checked at 400-4000cm^{-1}.

PREPERATION OF MICROSPHERES

Upheld microspheres containing cyclobenzaprine hydrochloride as an inside material was set up by "Non-Aqueous Emulsion Solvent Evaporation" system.

Eudragit RS-100 polymer microsphere preparation

- Firstly the medication was break down in polymer arrangement made by dissolving the polymer 2:1 blend of acetone and methanol.
- The above slurry was gradually brought into 75ml of light fluid paraffin containing range 80 (0.5%) as surfactant
- Stirred at 1100rpm and 2200rpm by mechanical stirrer furnished with 3 bladed propeller at room temperature.
- Stirring was proceeded for 3-4 hours.
- To permit the dissolvable (CH3)2CO and methanol) to dissipate totally.
- The microspheres were framed and they were gathered by filteration.
- The microspheres were washed with n-hexane or oil ether to expel the overabundance oil or to free from oil.
- The microspheres were drying at temperature which is of room.

Chitosan polymer microsphere preparation

- Chitosan arrangement (0.1%) was set up by dissolving 1g of chitosan in 900ml of refined water containing 10ml of frosty acidic corrosive with the guide of an attractive stirrer.
- Microspheres were set up by dissolvable vanishing strategy. 200ml of aqueous adhesive of Na-CMC (0.5%) was readied containing 1% v/v tween 80.
- At 100 rpm for 3 hours. Polymer was pour in 100ml of chloroform.
- After 3 hours of persistent blending finally the medication was involved.

Sodium alginate polymer microsphere preparation

- Method followed is section separation emulsion technique.
- Initially prepare a chemical compound resolution i.e. forty mg metallic element alginate in twenty metric capacity unit water taken in 50ml beaker.
- To this slowly add 20mg of drug (cyclobenzaprine hydrochloride).
- Allow it for stirring, beneath a mechanical stirrer for at least 10-15min.
- Due to excessive stirring, bubbles are going to be shaped within the resolution which might be removed by addition of 5mg S.L.S beneath a digital immoderate sonicator.
- Then in another beaker take five-hitter Cacl2 (i.e.; 5gm in 100ml H20) and blend it properly to work a uniform resolution.
- With facilitate of needle, add the ready chemical compound resolution drop wise into the $Cacl_2$solution.
- Transparent microbeads may be discovered within the $Cacl_2$solution, these micobeads are nothing however the microspheres
- Filter the answer to separate the microspheres
- The separated microspheres are unbroken aside until 15-20min for drying during a receptacle appliance at sixty degrees until all the wet is gaseous.
- Add Titanium dioxide to the higher than developed microspheres to create them stable for an extended length.

EVALUATION

The microspheres are assessed by the accompanying tests

Particle Size, Shape and Surface Morphology Analysis[12,13]

All the microspheres were assessed concerning their size and shape utilizing optical microscope

(OLYMPUS CH 20i) with adjusted programming magnus genius 3.0 and Olympus ace through a camera utilizing an amount of dried microspheres suspended in glycerin. The molecule widths of more than 100 microspheres were estimated arbitrarily by optical microscope. Scanning electron magnifying instrument was performed to portray formed microspheres. Examining Electron photomicrographs of drug-loaded microspheres.

Drug Polymer Interaction (FTIR) Study[14]

IR spectrometry is performed by Fourier modified infrared photometer. The pellets of medication and restrainer were got wind of by compacting the powders at twenty psi for ten min on KBr-press and also the spectra were examined within the oftenness scope of 4000- 600cm^{-1}. FTIR study was carried on pure medication, physical mix, plans and void microspheres.

Production Yield[15,16]

The generation yield of microspheres of various particularisation were determined utilizing the heaviness of last item within the wake of drying as for the underlying combination load of the medication. And p.c creation yield were determined consistent with the instruction documented beneath

$$\text{Production Yield} = \frac{\text{Practical mass of micorspheres}}{\text{Theoretical amount of drug and polymer}} \times 100$$

Swelling Study

The swell capacity of microspheres in physiological media was controlled by swelling them in the phosphate cradle (pH 7.4). Precisely gauged sums (50mg) of microspheres were inundated in minimal abundance of phosphate cushion (pH 7.4) in a petri dishes for 24 h. After that the swollen microspheres were isolated utilizing Whatmann channel paper. The wet load of the swollen microspheres was controlled by first blotching the particles with channel paper to expel retained water at first glance and afterward weighing promptly on an electronic equalization.

Determination of Drug Content

Precisely gauged up to ten mg muscle relaxant coordination compound microsphere and smashed in glass mortar and pestle. The fine microspheres poor down in a hundred milliliter fuel with the help of unhearable stirrer and therefore the arrangement was sifted through Whatmann channel paper, affordable weakening (2, 4, 6, 8, 10mcg/ml) created and evaluated the medication content ultraviolet light Spectrophotometrically.

Entrapment Efficiency[17]

Entrapment efficiency was calculated by the formula:

$$\text{Entrapment Efficiency} = \frac{\text{Amount of drug in microspheres}}{\text{Amount of drug in microsphere entrapped}}$$

Evaluating *In-vitro* Release Studies[18,19]

The medication discharge examine was performed utilizing USP XXIV bin mechanical assembly at 37°C ± 0.5°C at 50rpm utilizing 900mL of phosphate cradle (pH 6.8) as a disintegration medium (according to USP XXVI dissolution). Microspheres proportional to 10mg of Cyclobenzaprine hydrochloride sedate were utilized for the test. Five milliliters of test arrangement was pulled back at foreordained time interims, separated through a Whatmann channel paper, weakened reasonably, and broke down by spectrophotometric. An equivalent measure of new disintegration medium was supplanted following withdrawal of the test. Rate sedate broke down at various time interims was determined.

Kinetics of drug release

To take a gander at the drug release vitality and part, the total release data were fitted to models addressing Zero ask for (Q v/s. t), First ask for [Log (Q0□Q) v/s. t], Higuchi's square base of time (Q v/s. t ½) and Korsmeyer Peppas twofold log plot (log Q v/s. log t) independently, where Q is the aggregate dimension of medicine released at time t and (Q0□Q) is the consolidated dimension of drug remaining after time t.

To say it evidently, the results got from *in vitro* release considers were plotted in four vitality models of data treatment as seeks after.

- Cumulative rate steady release Vs. Time (Zero ask for rate vitality)
- Log joined rate steady held Vs. Time (First ask for rate vitality)
- Cumulative rate steady release Vs. √T (Higuchi's set up scattering condition)

- Log joined rate steady release Vs. log time (Korsmeyer Peppas condition)
- Active investigation was performed and the information was assessed in the wake of fitting to Zero request, First request, Higuchi, Peppas values watched were Regression co-effective ® and Diffusion example. Criteria for choosing most proper model depended on best unwavering quality of fit demonstrated by 'R' esteem closer to one. At the point when tranquilize discharge is focus reliant, first request display is a marker. Zero request models are free of focus of medication. Grid display is pertinent when network polymer is utilized and Peppas demonstrate is utilized when discharge component isn't notable, fickian dissemination exists when n<0.5, however at n>0.5, nonfickian dispersion system is watched.

Stability Studies[20]

Accelerated Stability Studies

Stability Definition Stability of a pharmaceutical arrangement can be characterized as "the ability of a specific plan (measurements shape or medication item) in an explicit compartment/conclusion framework to stay inside its physical, synthetic, microbiological, remedial and toxicological particulars all through its time.

Instability in present day plan is regularly imperceptible simply after significant capacity period under ordinary conditions. To evaluate the security of a detailed item it is regular to open it to high pressure conditions to improve disintegration and in this manner the time required for testing is decreased. Regular high pressure factors are temperature and dampness. This will wipe out unsuitable definition.

RESULTS AND DISCUSSION

Pre-formulation studies

Description

White, odorless powder

Identification of drug sample

Determination of λ max of Cyclobenzaprine hydrochloride

From the ultraviolet spectrophotometric analysis it absolutely was ended that the drug, Flexeril complex showed a λ good at 290nm that was similar with the rumored λ good of Flexeril complex (USP). Therefore, the discovered λ good was used for any experimental work to investigate the check samples.

Calibration curves in various media

The standardisation curves for Flexeril complex in 0.1 N HCl, phosphate buffer pH scale 7.4 and water were developed spectrophotometrically.

Preparation of ordinary graph of Flexeril complex in pH scale 7.4 buffer, 0.1N Hcl and in H_2O

Standard answer was ready by dissolving 10mg of Flexeril complex in distilled water/0.1N HCL/ pH scale 7.4 buffer in an exceedingly 100ml of meter flask. From the quality answer, variety of dilutions containing one 2, 3, 4, 5, 6, 7, 8, 9, and ten µg/ml.

Melting point

Melting point of cyclobenzaprine hydrochloride was determined by capillary method using the apparatus which is of melting.

Procedure

- Make the crystalline substance into powder form. Take one capillary tube and at the one end of capillary tube seal it by heating.
- Then on the open side of capillary tube fill it with powder substance.
- To fill the cylinder, make a stack of the powdered substance on the permeable plate. Push at another end of the narrow cylinder into the stack.
- A portion of the powdered substance will enter the capillary tube.
- At another side of the tube tap on permeable plate to fill powder substance. Till 2-3mm should be filled.
- After then put into fine cylinder to a thermometer utilizing a string.
- Take liquid paraffin in a compartment and place it over a touch of wire dressing set over a tripod stand.
- Take fluid paraffin in a measuring glass and place it over a bit of wire bandage put over a tripod stand.

- Clamp the thermometer conveying the test cylinder to an iron stand and submerge them in the shower of fluid paraffin.
- The surface strain of the shower fluid is adequate to hold the slender cylinder in position.
- Heat the container gradually while always mixing the substance utilizing a stirrer to keep up a uniform temperature all through.
- When the temperature is inside 15º of the dissolving purpose of the unadulterated substance, the fire is lessened at that point.

Result- melting point of cyclobenzaprine is 217°C

Solubility

Solubility might be characterized as the unconstrained cooperation of at least two substances to shape a homogeneous scattering. Around 5 mg of medication was added to 5ml of every dissolvable and sonicated for 10 minutes. The solubility was checked outwardly in all cases.

pH- Water-7, Ethanol-6

Assay-

Dissolve about 400mg cyclobenzaprine HCl accurately weighed. To determine end point take 80ml of G.A.A.in 15ml of mercury acetate and titrate it with 0.1perchloric acid. The end point was 10.5.

Partition co-efficient

- The established and most dependable technique is shake jar strategy.
- Break up a portion of the solute in a volume of octanol and water and after that shake the flask. Estimating the grouping of the solute in each solvent.
- Measuring the centralization of arrangement (by U.V/VIS).

CALCULATION

$K_{o/w}$ = [Co/Cw] at equilibrium

Dissolve 10mg drug in 20ml octanol and then add 20ml water and shake vigorously and leave it for 24 hours.

$K_{o/w}$ = [0.593/4] = 0.148

Micromeritics

Bulk density

Take 5g of drug accurately by weighing.

Fill the powder in measuring cylinder of 100ml capacity.

Note down the bulk volume of powder.

Observation

Weight of powder = M

Bulk volume of powder = V

Room temperature = 85°F, 29°C

Calculation

Bulk density = [mass of powder/bulk volume of powder]

Weight = 5g

Bulk = 16ml

Bulk density = [5/16] = 0.3125g/cm^3

Weight = 5g

Bulk = 18ml

Bulk density = [5/18] = 0.2777g/cm^3

Weight = 5g

Bulk = 20ml

Bulk density = [5/20] = 0.25g/cm^3

Average bulk density **=** 0.3125+0.2777+0.25/3 = 0.28006g/cm^3.

Result

The bulk density was 0.2800g/cm^3.

Tapped density

Take 5g of drug accurately by weighing.

Fill the powder in 100ml capacity measuring cylinder.

Start tapping till count 100.

Note the bulk volume after tapping.

Or the bulk volume is determined by dropping the cylinder on the wooden surface three times height about 1inch for 2 min.

Observation

Weight of powder = 5g

No. of tapping = 100

Room temperature = 85°F, 29°C

Tapped density = [mass of powder/tapped volume of powder]

Weight = 5g

Tapped 11ml

Tapped density = [5/12] = 0.4166g/cm^3

Weight = 5g

Tapped= 11ml

Tapped density = [5/11] = 0.4545g/cm^3
Weight = 5g
Tapped = 9ml
Tapped density = [5/9] = 0.55g/cm^3
Average tapped density = [0.4166+0.4545+0.555/3] = 0.4737g/cm^3

Result

The tapped density was 0.4737g/cm^3.
Carr's index- Tapped density = 0.4737g/cm^3
Bulk density = 0.2800g/cm^3

Calculation

Carr's index= [tapped density- bulk density/tapped density X 100] = [0.4737-0.2800/0.4737 X 100] = 40.89%

Result

The compressibility index was 40.89%.
Hence the type of flow of powder is poor.
Hasuner's ratio- Tapped density = 0.4737g/cm^3
Bulk density = 0.2800g/cm^3

Calculation

Hasuner's ratio = [tapped density/bulk density] [0.4737/0.2800] = 1.69%

Result

Hasuner's ratio was 1.69%, therefore it indicates poor flow.

Compressibility

Take the measuring cylinder
Place it on the plane surface
Powder is added using glass funnel
Measure the bulk volume
Tap the measuring cylinder using tapping
Record the volume after tapping

Compressibility index

Result

Compressibility index of powder after 50 times tapping was 54.9%. Hence the flow of powder is very poor.

Angle of repose

Place the glass funnel on a ring supported by stand
Take 5g of powder sample
Block the orifice of the funnel by thumb
Fill the powder in funnel and remove thumb immediately
Maintain the gap between the bottom of the funnel and top of the powder pile
Begin streaming the powder from the channel, at that point a powder pile will be framed, the stature of the powder pile is then estimated.

Result

The angle of repose was 48.0663. Hence the flow property is very poor.

Similarity examines were performed utilizing FT-IR spectrophotometer to discover any physical and in addition substance modification of the medication attributes. The unadulterated medication and blend of polymer and medication their IR spectra were examined. In the outcomes, it was chosen that there was no obstruction found in useful gathering and in the pinnacles of Cyclobenzaprine hydrochloride was observed to be immaculate in the medication polymer blend, demonstrates that they were impeccable.

Stability Study

The steadiness investigations of definition F1 to F2 were done at 45° C ± 2°C 75% ± 5% RH and spillage of the medication from the microspheres were examined regarding rate tranquilize content.

The outcomes appearing in F5 plan of cyclobenzaprine hydrochloride polymer sodium alginate microsphere was observed to be steady for around 3 months without demonstrating any adjustments in medication content.

Table No.1: Standard Curve in Distill water, 0.1N HCl, and in pH 7.4 buffer

S.No	Concentration µg/ml	Absorbance in Distill water	Absorbance in 0.1N HCl	Absorbance in pH 7.4 Buffer
1	0	0	0	0
2	5	0.049	0.040	0.070
3	10	0.093	0.079	0.140
4	15	0.135	0.116	0.201
5	20	0.168	0.152	0.273
6	25	0.209	0.185	0.360

Table No.2: Solubility profile of Cyclobenzaprine hydrochloride

S.No	Solvent	Solubility
1	Distilled water	Very soluble
2	Ethanol	Freely soluble
3	Isopropanol	Sparingly soluble
4	Methylene chloride	Slightly soluble
5	Hydrocarbon	Insoluble

Table No.3: Bulk density

S.No	Weight	Bulk	Bulk density	Average bulk density
1	5g	16ml	0.3125 g/cm^3	0.2800g/cm^3
2	5g	18ml	0.2777g/cm^3	
3	5g	20ml	0.25 g/cm^3	

Table No.4: Tapped density

S.No	Weight	Tapped	Tapped density	Average tapped density
1	5g	10ml	0.4166 g/cm^3	0.4737g/cm^3
2	5g	11ml	0.4545 g/cm^3	
3	5g	9ml	0.55g/cm^3	

Table No.5: Compressibility index

S.No	% Compressibility	Flow ability
1	< 40	Very very Poor
2	33 – 37	Very Bad
3	23 – 35	Bad
4	18 – 21	Fair Passable
5	12 – 16	Good
6	5 – 12	Excellent

Table No.6: Angle of repose as an indication of powder flow properties

S.No	Angle of Repose	Type of Flow
1	> 40	Very very poor
2	34 – 38	Very Bad
3	30 – 34	Fair
4	20 – 30	Good
5	< 20	Excellent

Particle Size

Table No.7: Particle size

Formulation code	Mean particle size		
	Eudragit RS100	Chitosan	Sodium alginate
F1	316.15	262.50	128.23
F2	342.89	297.70	185.15
F3	371.28	335.39	248.63
F4	389.72	357.21	268.37
F5	398.38	375.95	283.40

Practical yield

Table No.8: Practical yield of Eudragit, Chitosan, sodium alginate

Formulation code	Practical yield		
	Eudragit RS100	Chitosan	Sodium alginate
F1	72.56	87.28	67.48
F2	80.83	91.53	74.73
F3	83.28	94.39	79.18
F4	87.34	96.17	83.33
F5	91.20	99.60	89.70

Percentage Drug content

Table No.9: Percentage drug content Eudragit RS-100, Chitosan, sodium alginate

Formulation code	Practical yield		
	Eudragit RS100	Chitosan	Sodium alginate
F1	87.64	77.68	85.76
F2	90.47	85.54	83.11
F3	89.84	80.67	86.81
F4	88.84	87.99	91.33
F5	92.63	83.50	95.70

Drug entrapment efficiency

Table No.10: Drug entrapment efficiency of Eudragit RS100, Chitosan, Sodium alginate

Formulation code	Drug entrapment efficiency		
	Eudragit RS100	Chitosan	Sodium alginate
F1	65.74	68.17	78.33
F2	69.24	74.11	83.11
F3	74.57	78.22	86.31
F4	78.07	81.66	88.33
F5	80.83	84.00	89.70

Swelling index

Table No.11: Swelling index of Eudragit-RS 100

Formulation	Swelling index (mg)
F1	0.50
F2	0.74
F3	0.87
F4	0.95
F5	1.22

Table No.12: Swelling index of Chitosan

Formulation	Swelling index (mg)
F1	0.35
F2	0.37
F3	0.42
F4	0.48
F5	0.55

Table No.13: Swelling index of Sodium alginate

Formulation	Swelling index (mg)
F1	0.80
F2	0.94
F3	1.12
F4	0.90
F5	1.30

Table No.14: Interpretation of FT-IR spectra of cyclobenzaprine hydrochloride

S.No	Functional category	Standard IR range (cm^1)	Assessment of peak in drug (cm^{-1})
1	Skeletal ring stretching vibration in aromatic ring.	1300-1600	1319.35, 1435.09, 1530.57, 1594.22
2	C-H stretching in aromatic ring	3000-3100	3060.17
3	Overtone of C-H bending in aromatic ring	1600-2000	1790.17
4	C-H Symmetric stretching of -CH2 group in tertiary amine	2660-2820	2635.81
5	C-H bending vibration of –CH2 group in tertiary amine	1445-1485	1481.38
6	C-N stretching	1020-1220	1167.94
7	C-H in-plane bending in cycloheptane ring	722 or less	689.57

Table No.15: Compatibility studies

S.No	Functional category	Standard IR range (cm^1)	Ranges of peak in mixture (cm^{-1})
1	Skeletal ring stretching vibration in aromatic ring.	1300-1600	1345.37, 1439.91, 1470.77, 1510.22
2	C-H stretching in aromatic ring	3000-3100	2890.43
3	Overtone of C-H bending in aromatic ring	1600-2000	1649.19
4	C-H Symmetric stretching of -CH2 group in tertiary amine	2660-2820	2637.74
5	C-H bending vibration of -CH2 group in tertiary amine	1445-1485	1470.77
6	C-N stretching	1020-1220	1099.46
7	C-H in-plane bending in cycloheptane ring	722 or less	671.25

Dissolution Study

Table No.16: *In vitro* drug release of sodium alginate microspheres

Time in hrs	Formulation Code				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	34.04	30.68	28.92	22.48	21.46
2	41.16	36.92	30.06	28.85	25.46
3	49.52	42.08	40.56	37.95	35.93
4	57.04	51.88	49.00	43.24	41.41
5	63.64	59.72	57.84	51.84	49.42
6	72.08	65.26	66.64	60.53	57.34
7	74.27	69.24	74.04	68.84	64.94
8	79.90	75.28	78.64	71.48	78.48
9	80.15	77.65	80.38	73.95	82.98
10	89.90	81.64	82.47	77.95	85.85
11	95.30	95.66	95.14	80.04	87.95
12	98.27	99.84	97.12	82.36	89.83

Table No.17: Kinetic of drug release of sodium alginate

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Hixoncrowell R^2	Korsmeyer-peppas R^2
F1	0.923	0.953	0.991	0.804	0.651
F2	0.943	0.974	0.91	0.958	0.977
F3	0.981	0.910	0.981	0.830	0.746
F4	0.990	0.86	0.926	0.933	0.942
F5	0.993	0.822	0.935	0.921	0.951

Table No.18: Drug release of Eudragit Rs-100 microspheres

Time in hrs	Formulation Code				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	38.51	34.19	26.08	25.75	12.16
2	49.07	44.55	33.95	33.75	18.0
3	56.82	50.41	38.89	38.28	24.26
4	67.22	55.68	43.57	43.38	31.42
5	76.44	63.00	50.57	49.07	34.29
6	85.50	70.45	54.70	53.28	39.51
7	90.90	73.37	59.49	57.38	44.36
8	95.90	82.60	61.61	63.28	45.54
9	96.00	89.25	68.92	68.43	50.88
10	96.25	98.10	74.54	73.60	53.79
11	96.59	98.38	78.38	76.20	55.29
12	97.10	98.58	82.16	79.45	58.55

Table No.19.a: Drug release of Eudragit Rs-100 microspheres

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Hixoncrowell R^2	Korsmeyer-Peppas R^2
F1	0.903	0.973	0.994	0.973	0.840
F2	0.933	0.883	0.926	0.928	0.880
F3	0.920	0.977	0.979	0.966	0.919
F4	0.980	0.946	0.929	0.927	0.824
F5	0.969	0.987	0.979	0.982	0.931

Table No.19.b: Drug release of polymer Chitosan microspheres *in vitro*

Time in hrs	Formulation Code				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	41.04	32.88	27.12	21.12	15.48
2	46.32	40.32	34.56	24.60	17.52
3	51.37	45.96	39.61	27.96	23.09
4	55.94	51.12	43.81	32.41	31.20
5	63.38	58.92	49.70	36.61	34.09
6	71.31	63.24	57.38	41.30	35.17
7	77.20	70.44	59.07	43.82	40.10
8	82.85	76.56	60.40	47.55	43.22
9	86.10	82.44	65.08	51.75	46.59
10	90.43	86.88	67.01	54.64	49.71
11	91.28	90.37	70.14	60.76	53.32
12	92.49	94.33	71.11	63.17	57.28

Table No.20: Kinetic of drug release of polymer Chitosan microspheres

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Hixoncrowell R^2	Korsmeyer-Peppas R^2
F1	0.865	0.978	0.882	0.956	0.979
F2	0.926	0.942	0.921	0.964	0.987
F3	0.868	0.989	0.906	0.924	0.990
F4	0.943	0.983	0.929	0.974	0.973
F5	0.955	0.991	0.92	0.986	0.967

Stability Profile

S.No	Study	Storage Condition	Minimum Period
1	Long term	25ºC ± 2ºC hour ± five-hitter RH	12 months
2	Intermediate	30ºC ± 2ºC sixty fifth ± five-hitter RH	6 months
3	Accelerated	40ºC ± 2ºC seventy fifth ± five-hitter RH	6 months

Table No.21: Stability study for F5 formulation

S.No	Formulations	Before storage	Stored at 40°C ± 2°C and 75% ± 5% RH		
			1st month	2nd month	3rd month
1	F5	95.70±0.74	94.70±0.74	93.70±0.74	92.70±0.74

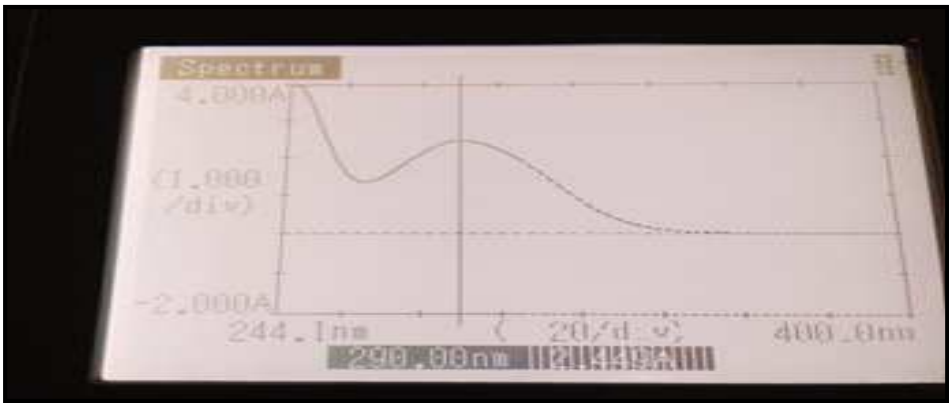


Figure No.1: U.V Scan of Cyclobenzaprine hydrochloride

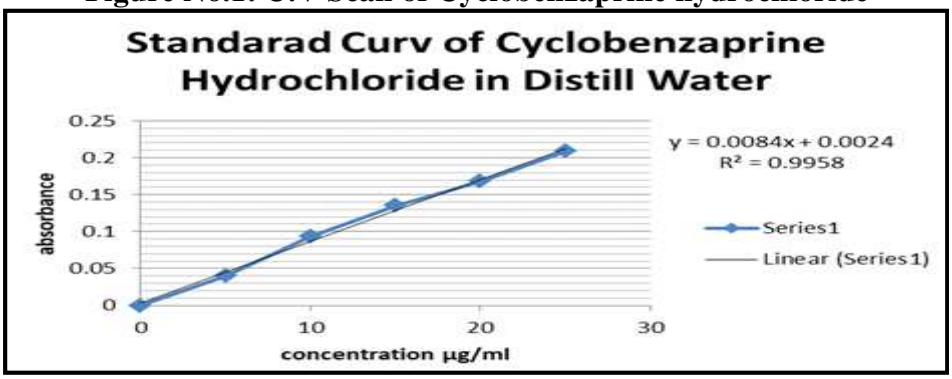


Figure No.2: Standard Curve in distill water

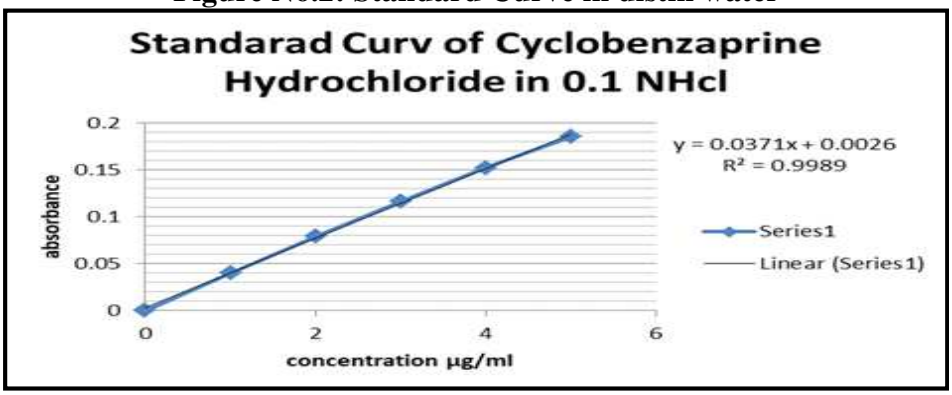


Figure No.3: Standard Curve in 0.1 N HCl

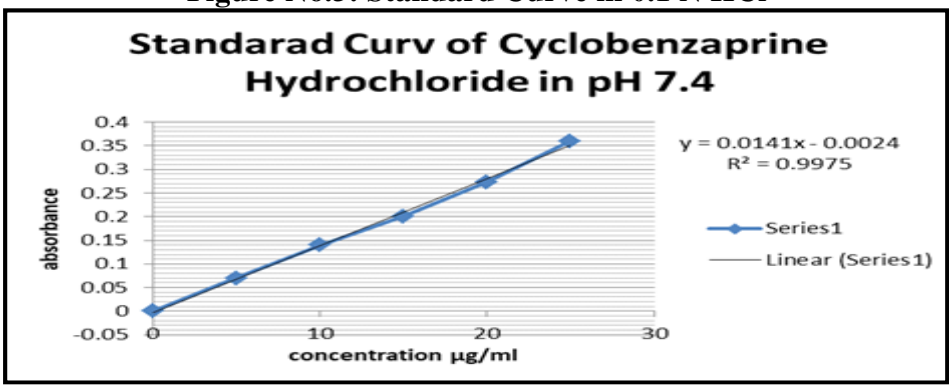


Figure No.4: Standard Curve in pH 7.4

Shape

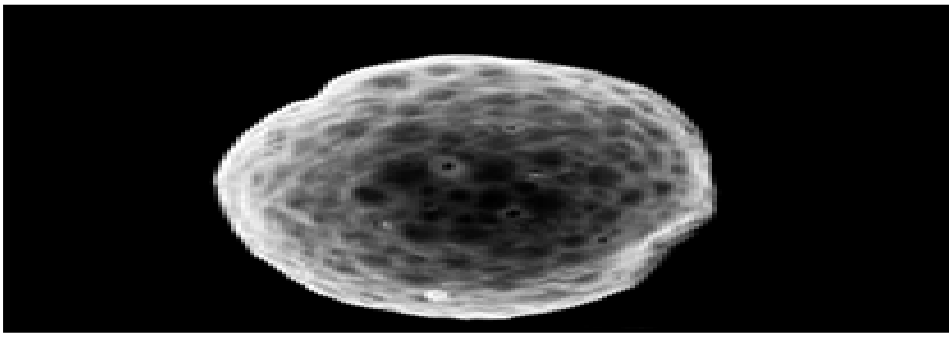


Figure No.5: Optical view of microsphere

SEM

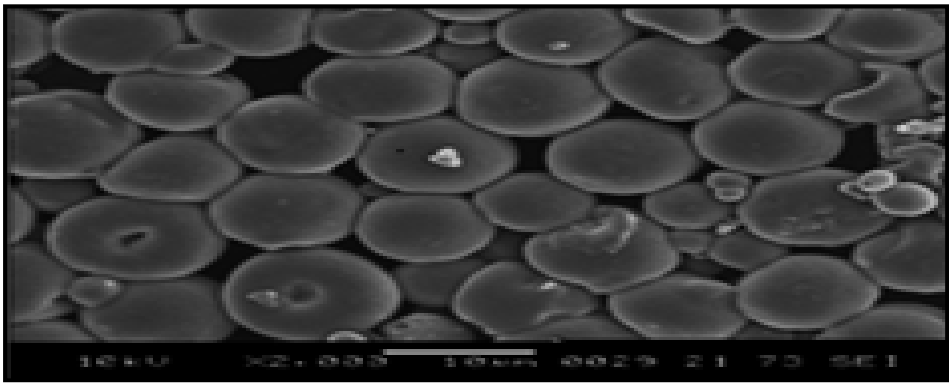


Figure No.6: SEM photomicrograph of sodium alginate

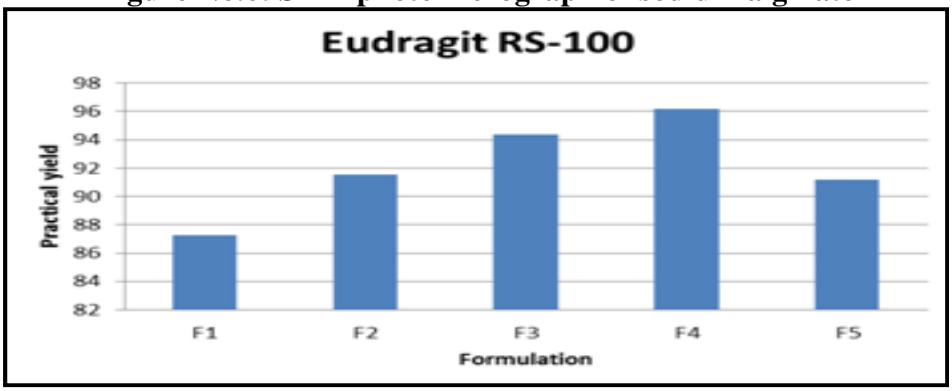


Figure No.7: Practical yield of Eudragit

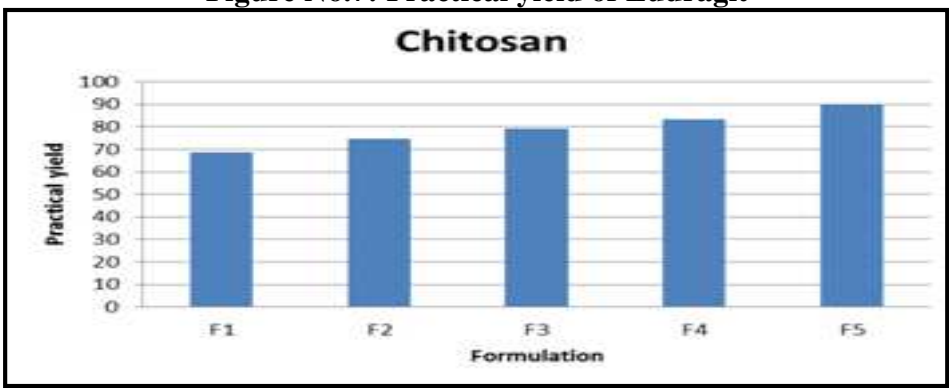


Figure No.8: Practical yield of Chitosan

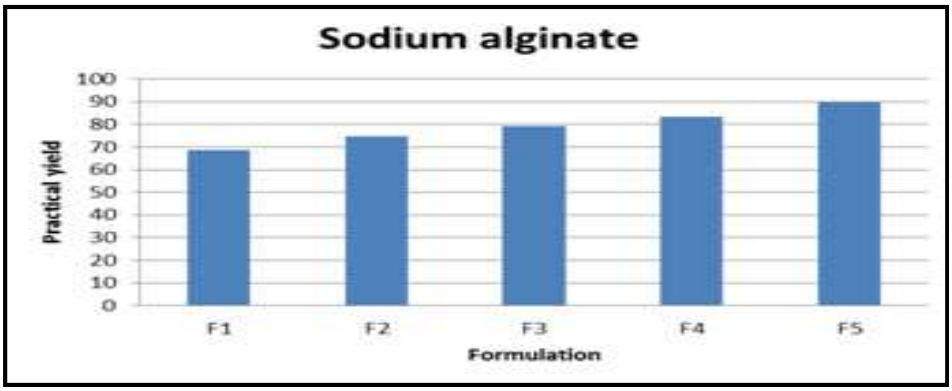


Figure No.9: Practical yield of Sodium alginate

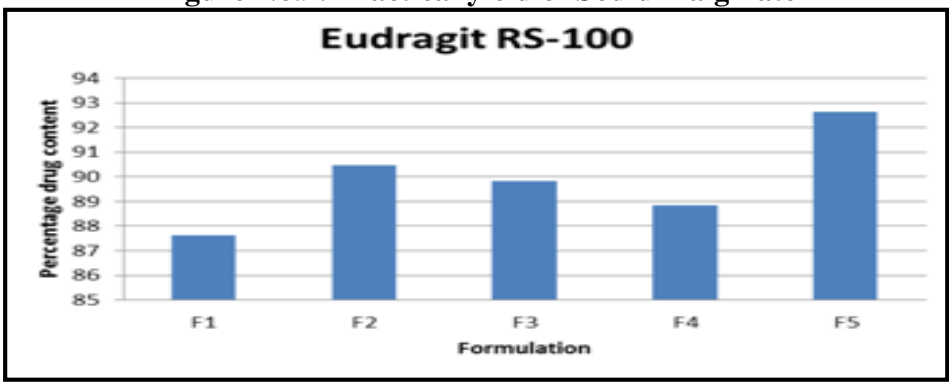


Figure No.10: Percentage drug content Eudragit RS-100

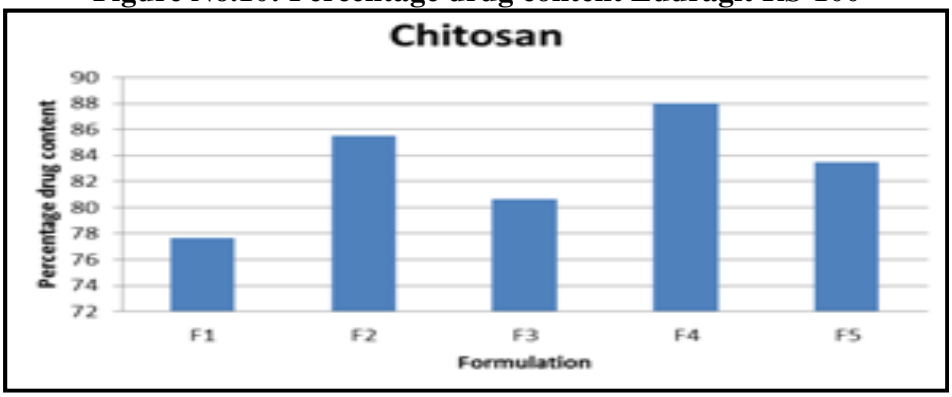


Figure No.11: Percentage drug content Chitosan

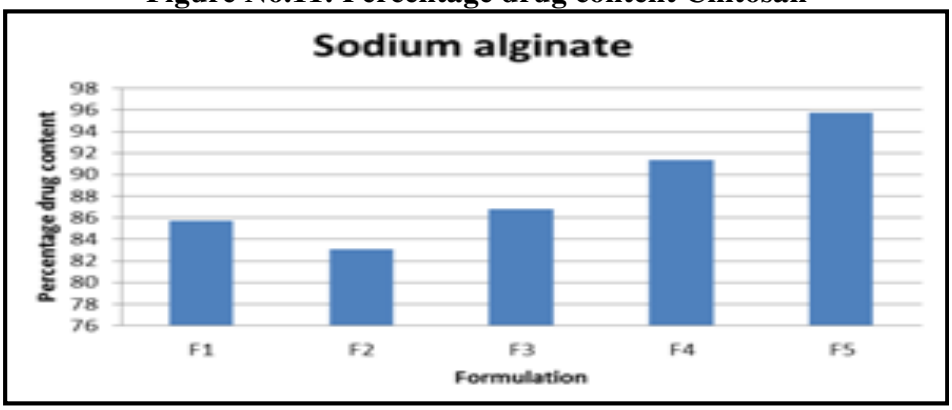


Figure No.12: Percentage drug content Sodium alginate

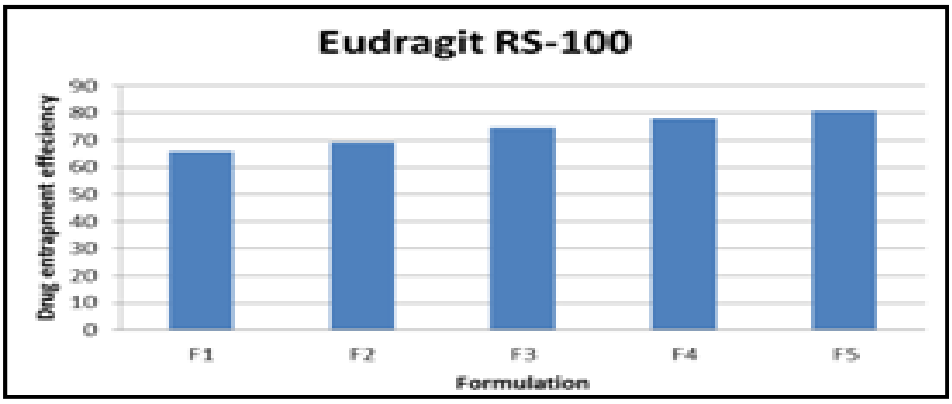


Figure No.13: Drug entrapment of Eudragit RS-100

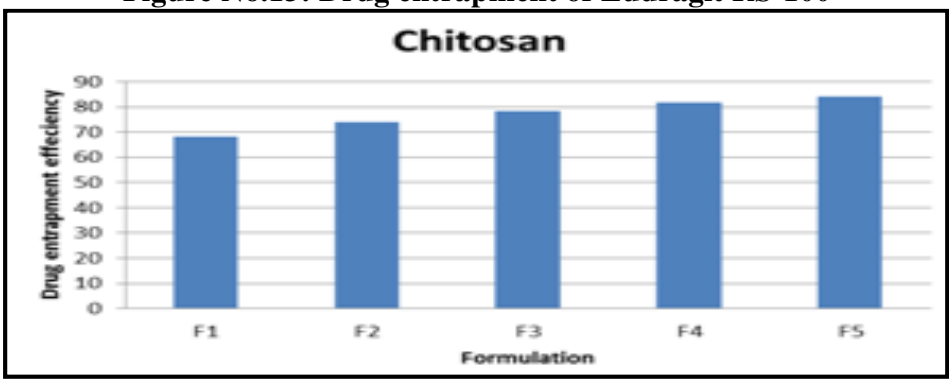


Figure No.14: Drug entrapment of Chitosan

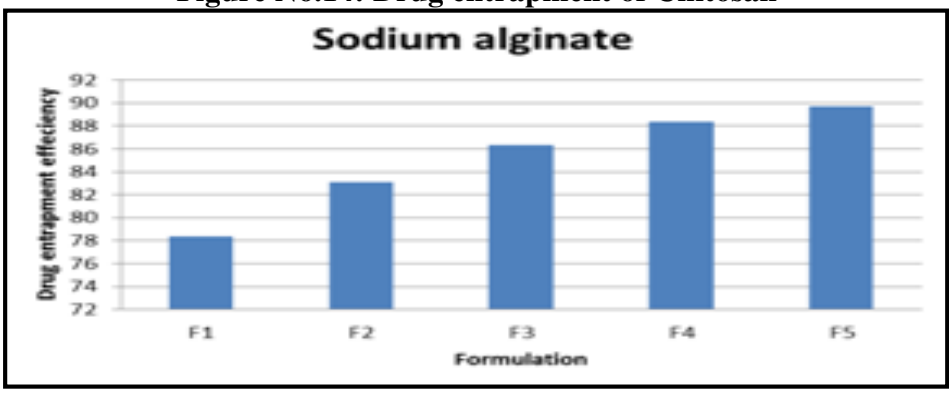


Figure No.15: Drug entrapment of sodium alginate

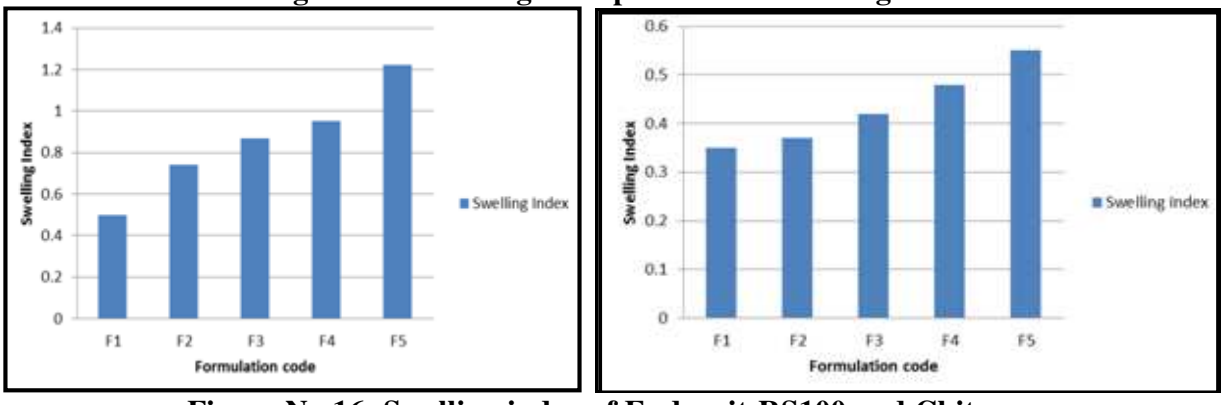


Figure No.16: Swelling index of Eudragit-RS100 and Chitosan

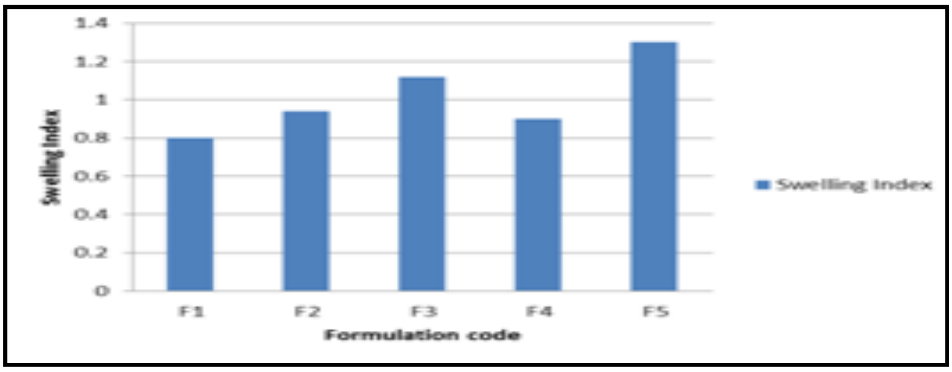


Figure No.17: Swelling index of Sodium alginate

FTIR, Interpretation, Compatibility

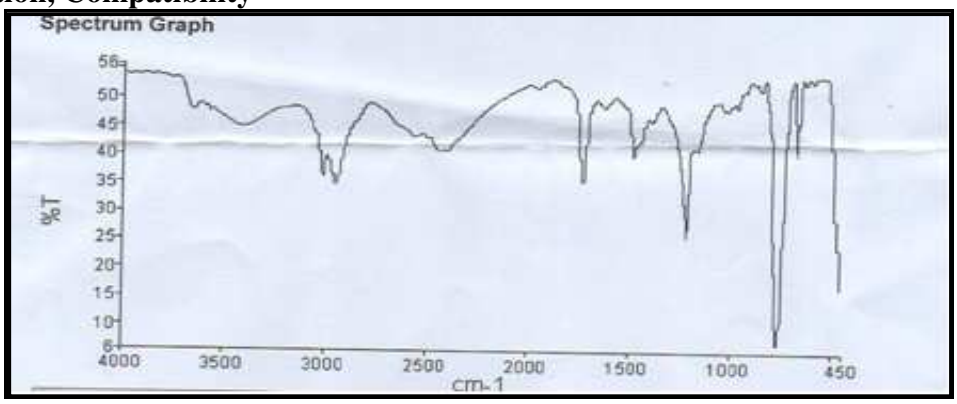


Figure No.18: IR Cyclobenzaprine hydrochloride

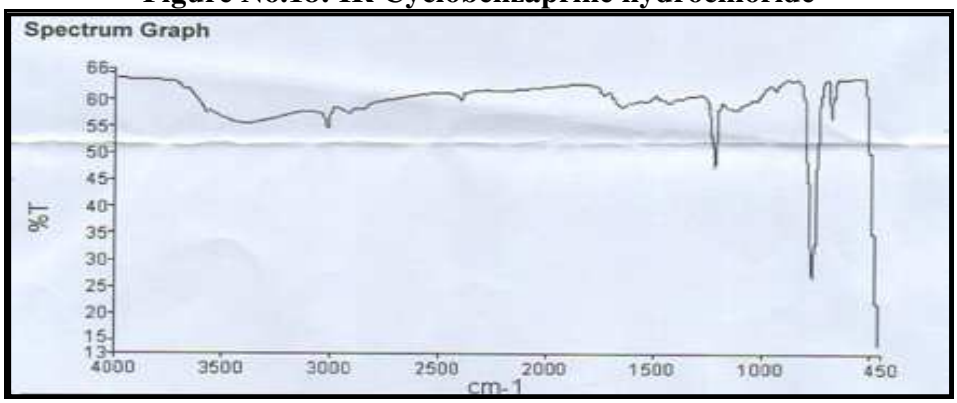


Figure No.19: IR Eudragit RS-100

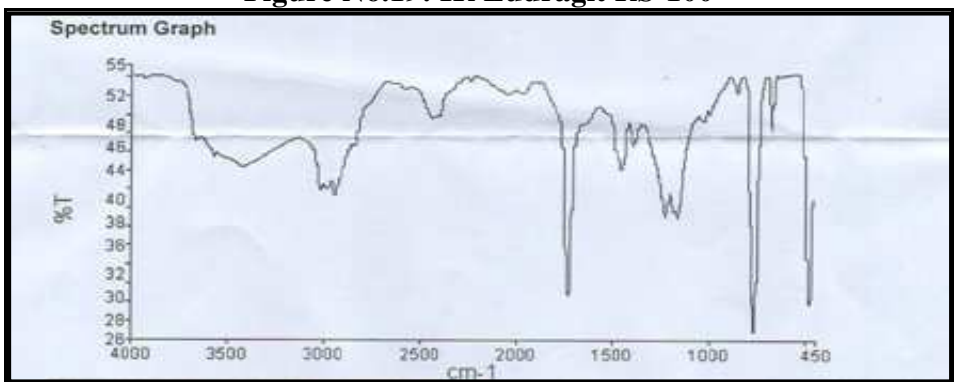


Figure No.20: IR Chitosan

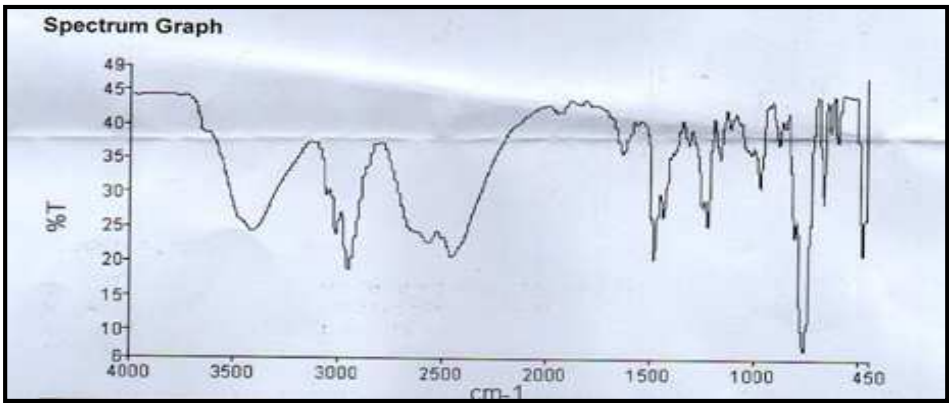


Figure No.21: IR Sodium alginate

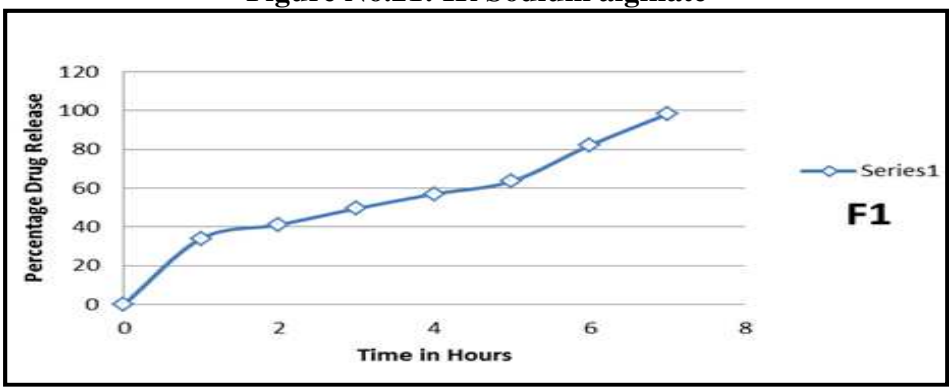


Figure No.22: Drug release of sodium alginate microspheres F1 *In vitro*

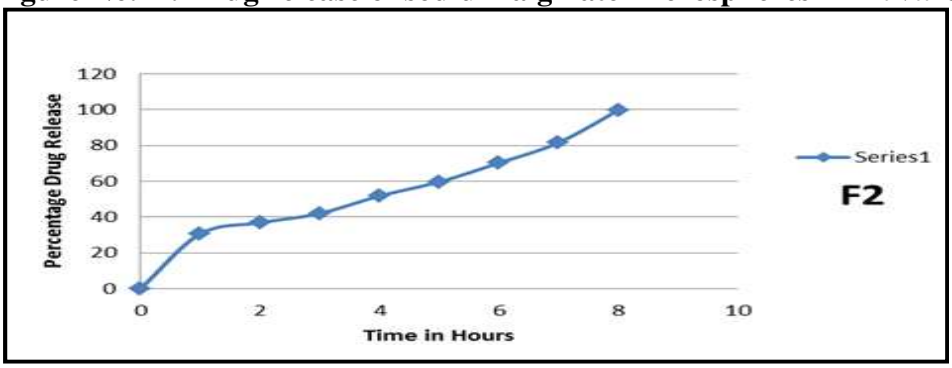


Figure No.23: Drug release of sodium alginate microspheres F2 *In vitro*

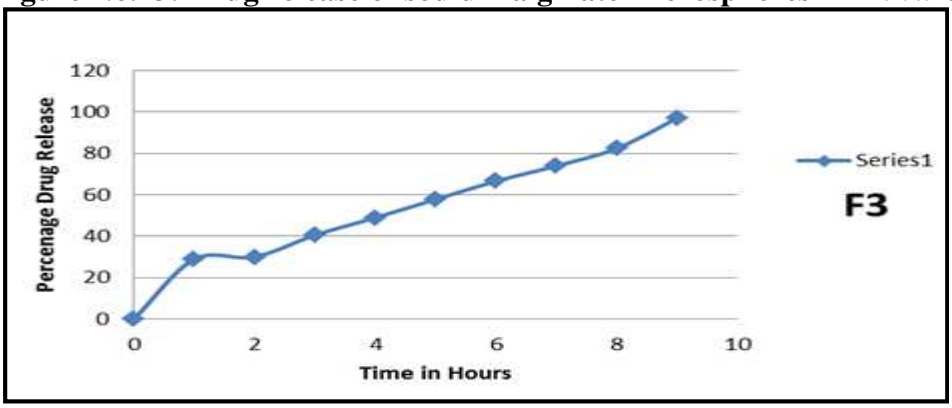


Figure No.24: Drug release of sodium alginate microspheres F3 *In vitro*

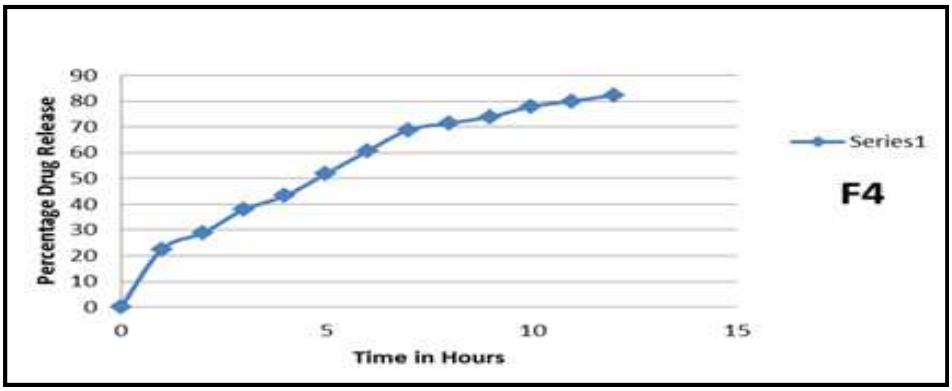


Figure No.25: Drug release of sodium alginate microspheres F4 *In vitro*

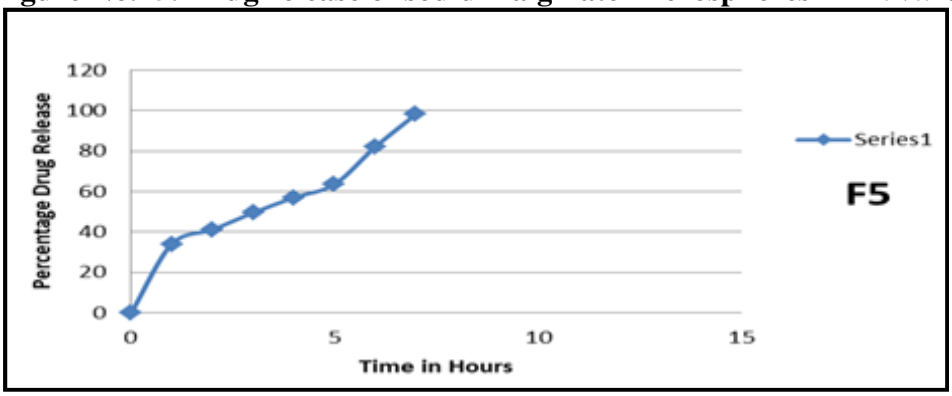


Figure No.26: Drug release of sodium alginate microspheres F5 *In vitro*

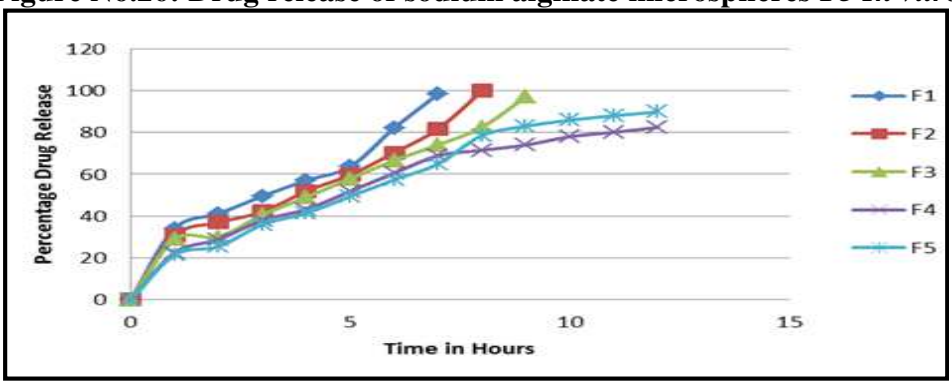


Figure No.27: Drug release presenting all 5 formulations *In vitro*

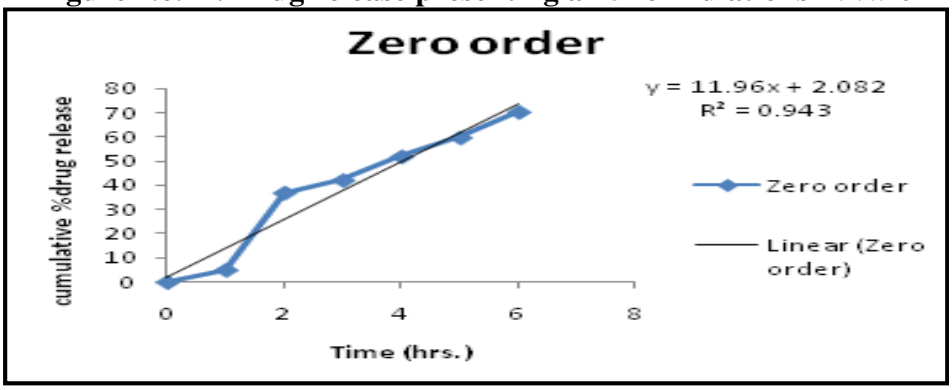


Figure No.28: Zero order kinetic

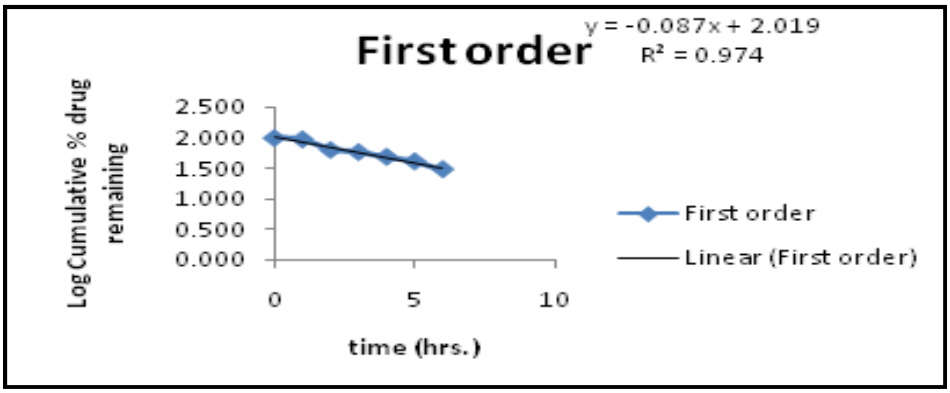


Figure No.29: First order kinetics

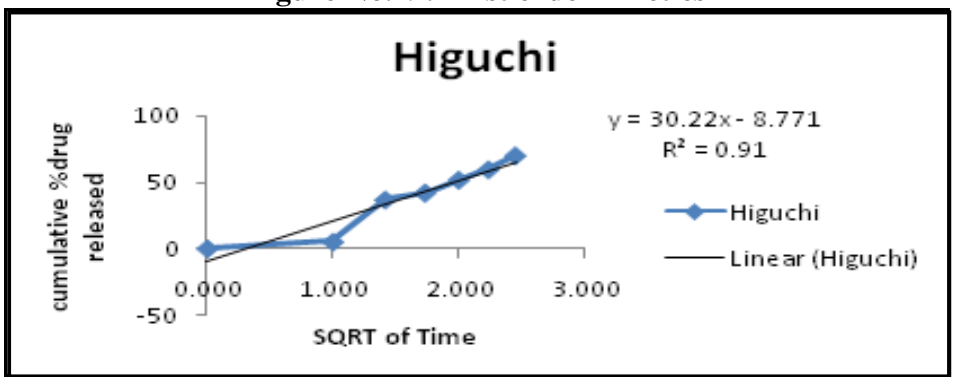


Figure No.30: Higuchi

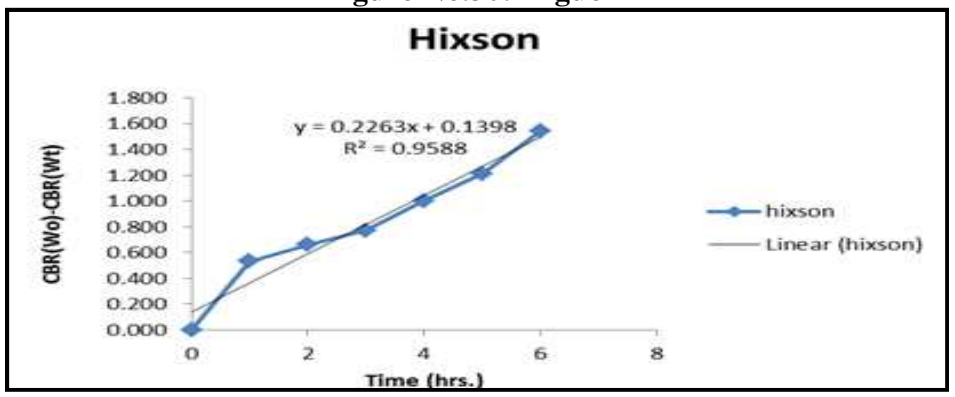


Figure No.31: Hixson

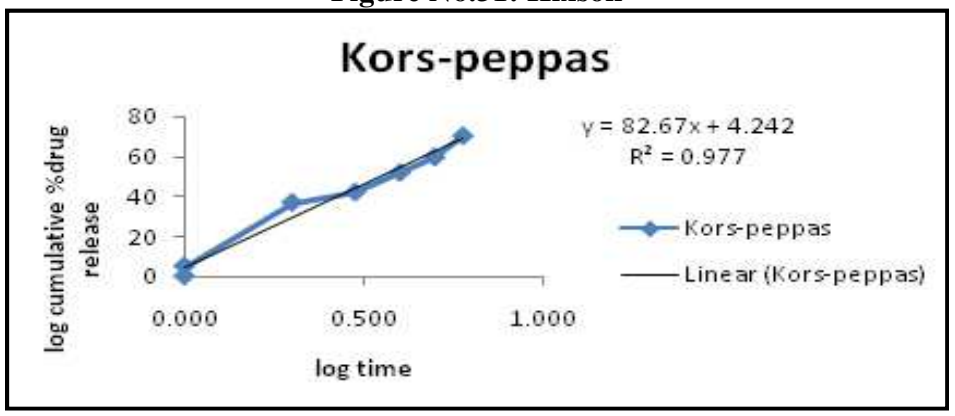


Figure No.32: Kors-Peppas

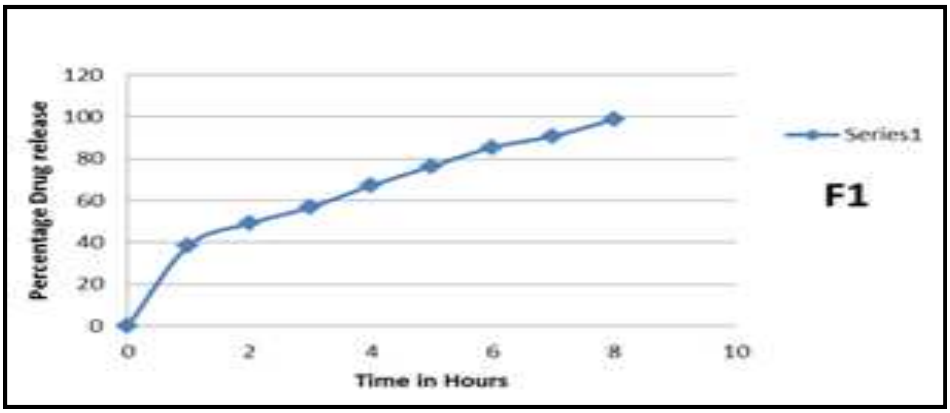


Figure No.33: Drug release of polymer EU Rs-100 microspheres F1

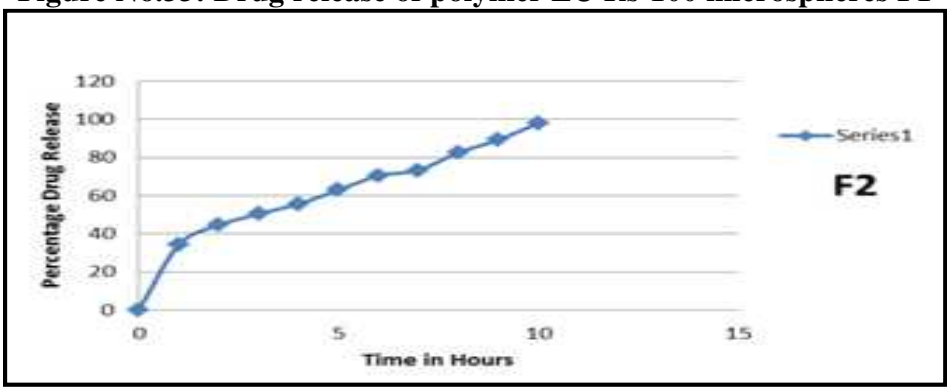


Figure No.34: Drug release of polymer EU Rs-100 microspheres F2

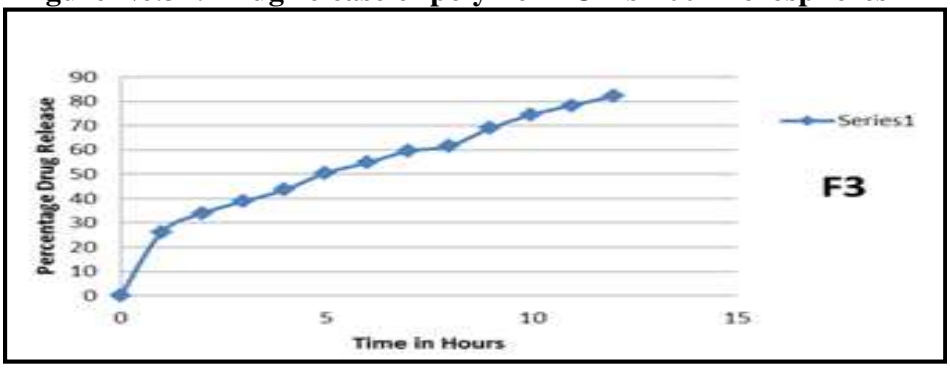


Figure No.35: Drug release of polymer EU Rs-100 microspheres F3

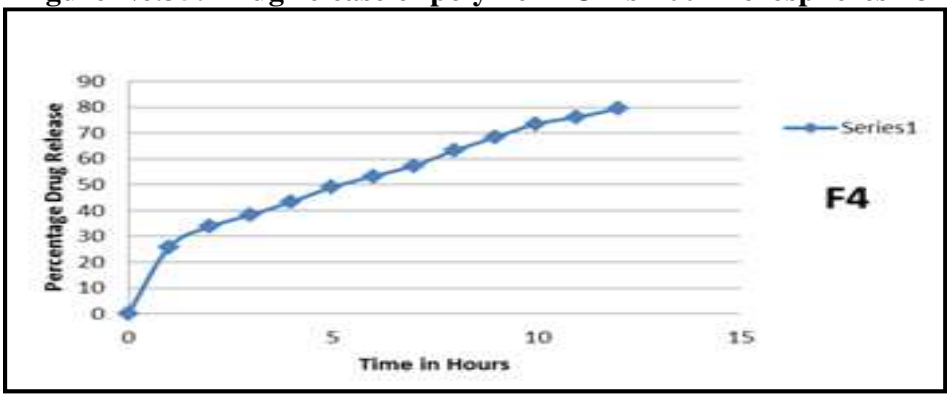


Figure No.36: Drug release of polymer EU Rs-100 microspheres F4

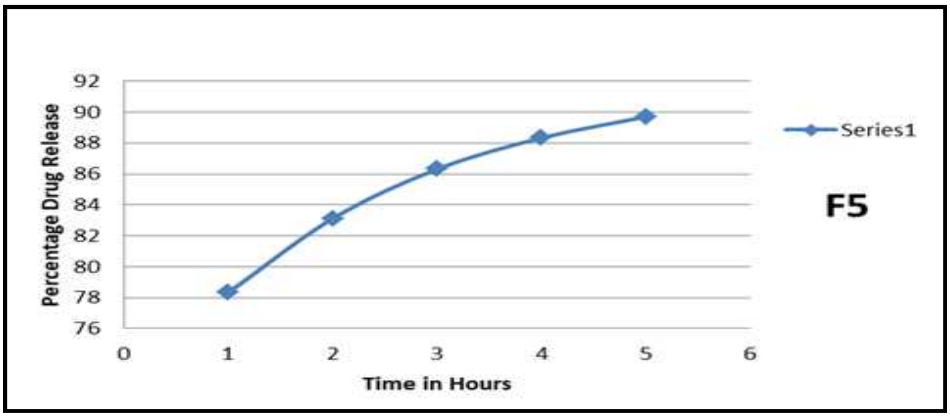


Figure No.37: Drug release of polymer EU Rs-100 microspheres F5

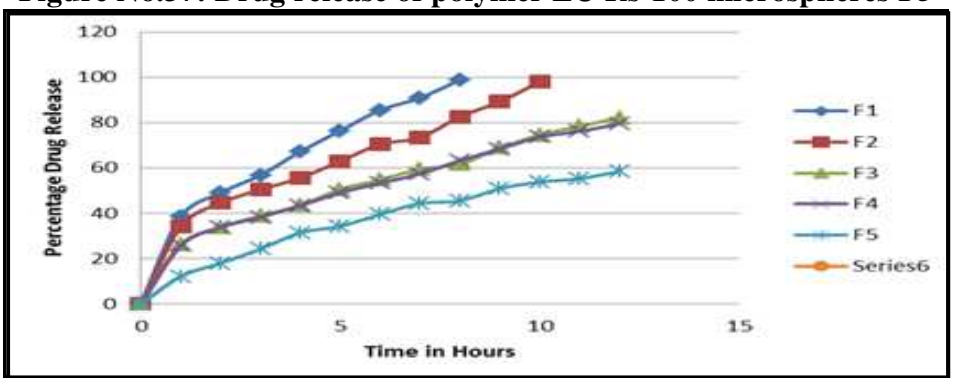


Figure No.38: Drug release presenting of polymer EU Rs-100 microspheres of all 5 formulations

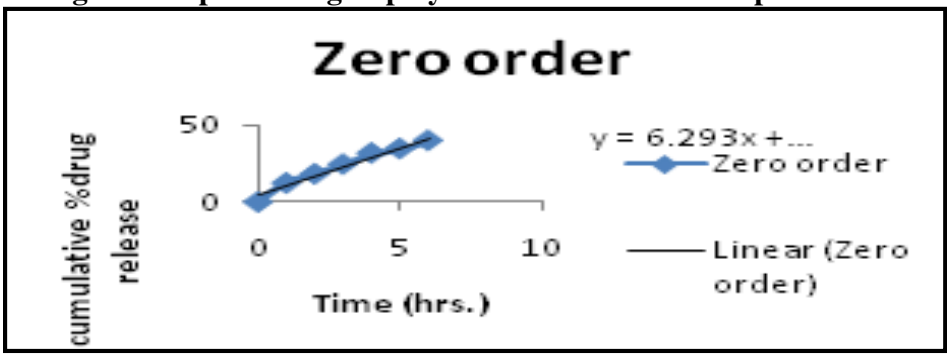


Figure No.39: Zero order kinetics

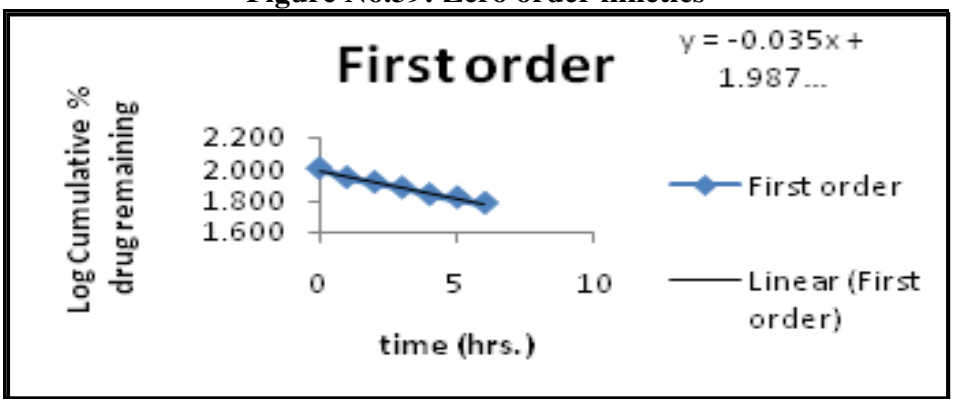


Figure No.40: First order kinetics

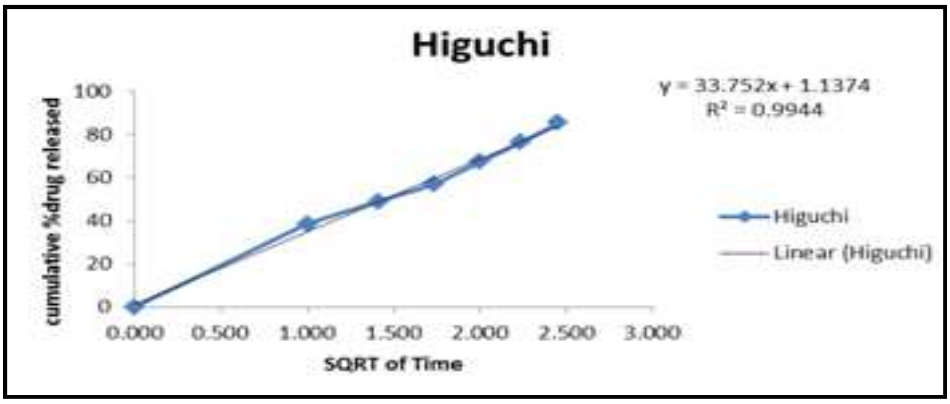


Figure No.41: Higuchi

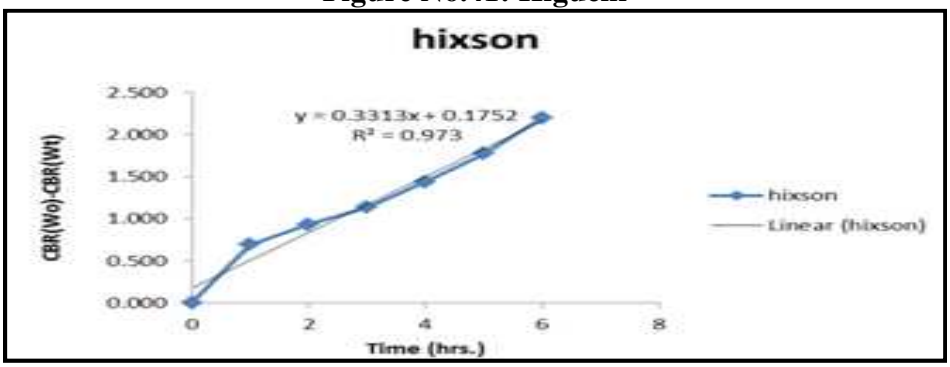


Figure No.42: Hixson

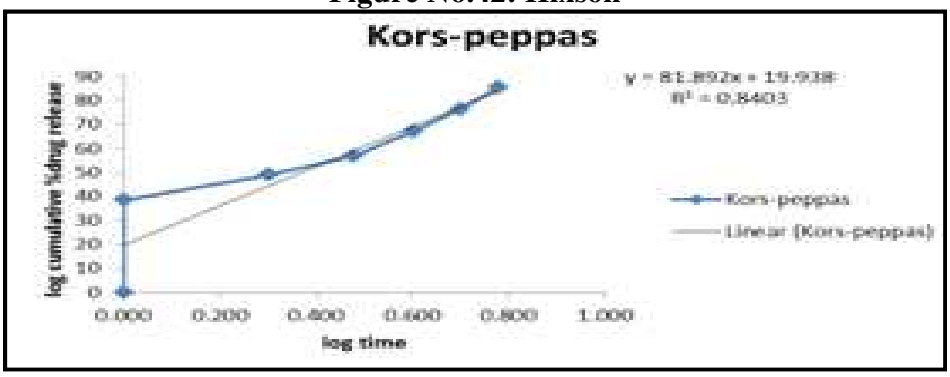


Figure No.43: Kors-Peppas

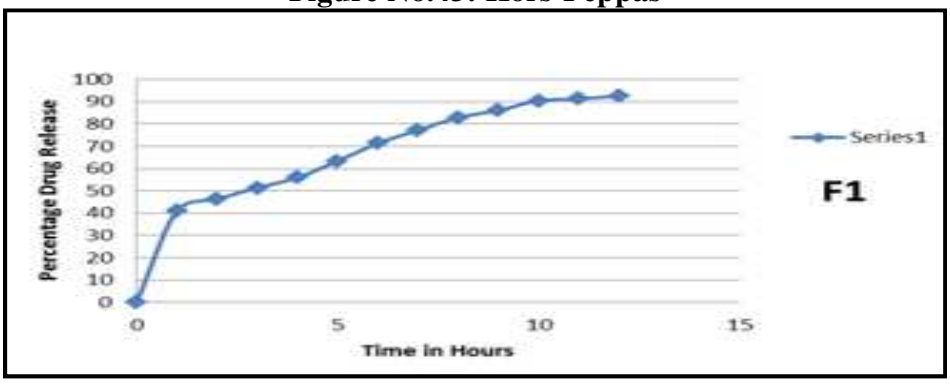


Figure No.44: Drug release of polymer Chitosan microspheres F1 *In vitro*

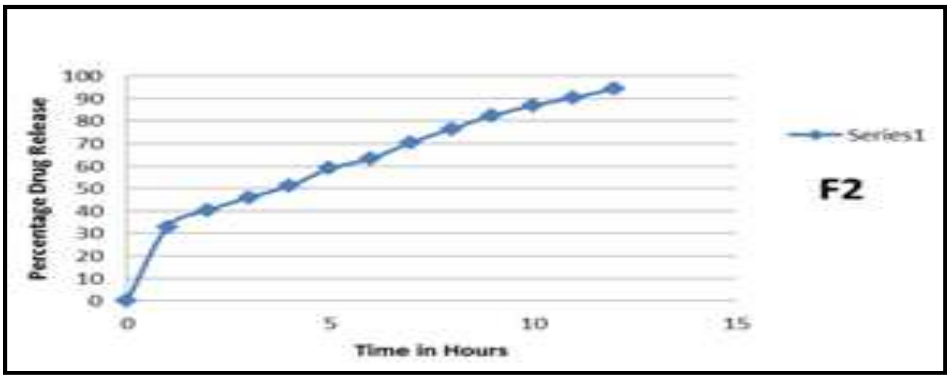


Figure No.45: Drug release of polymer Chitosan microspheres F2 *In vitro*

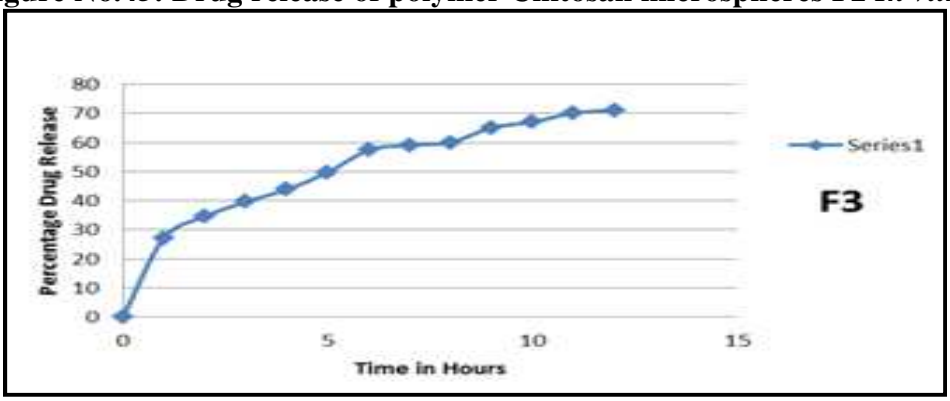


Figure No.46: Drug release of polymer Chitosan microspheres F3 *In vitro*

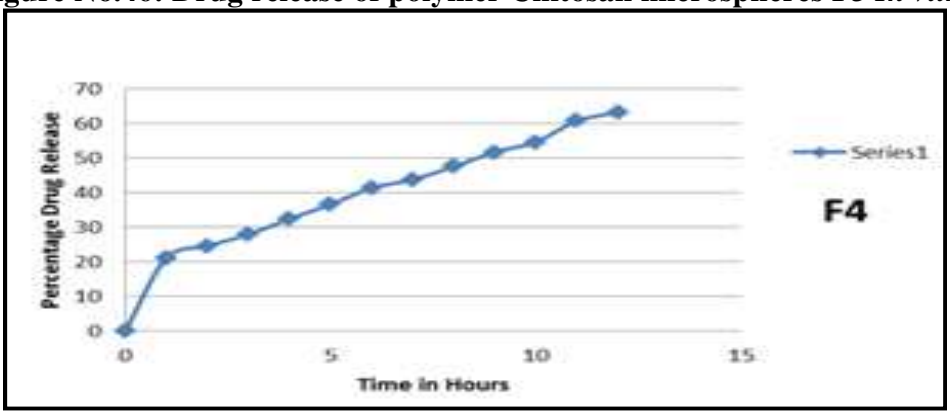


Figure No.47: Drug release of polymer Chitosan microspheres F4 *In vitro*

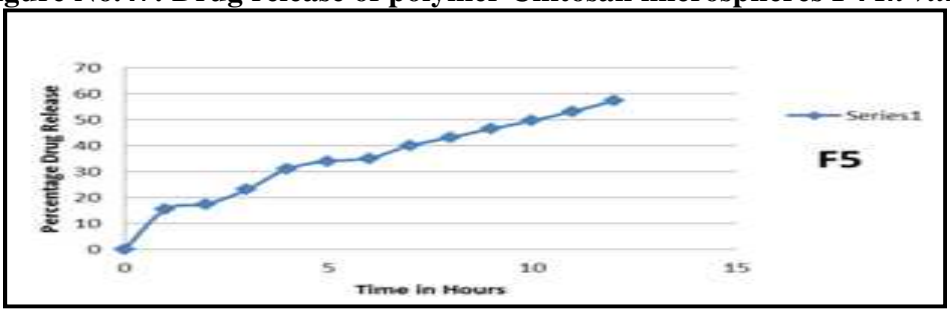


Figure No.48: Drug release of polymer Chitosan microspheres F5 *In vitro*

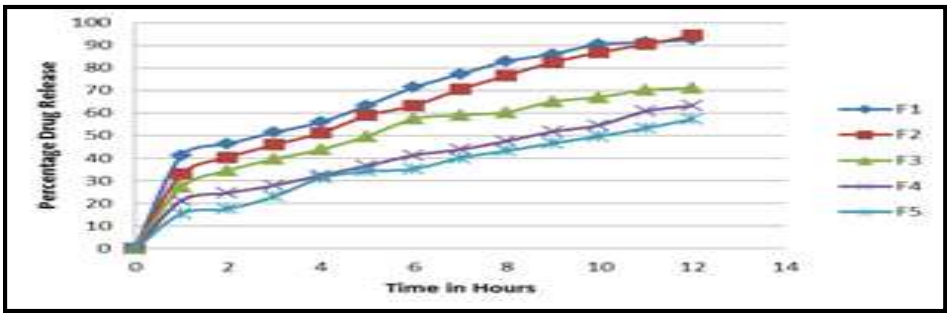


Figure No.49: Drug release presenting polymer of Chitosan microspheres of all 5 formulations

Figure No.50: Zero order

Figure No.51: First order

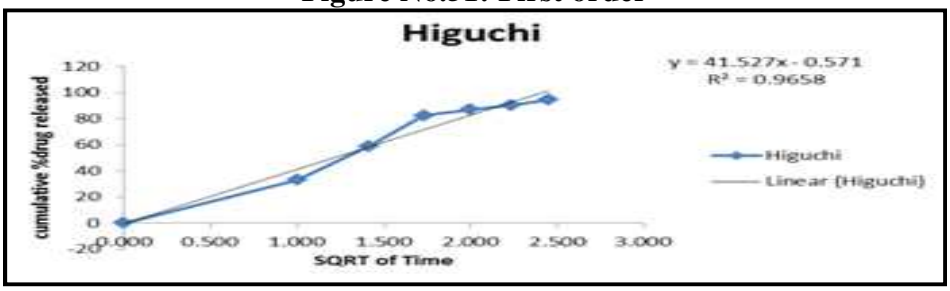


Figure No.52: Higuchi

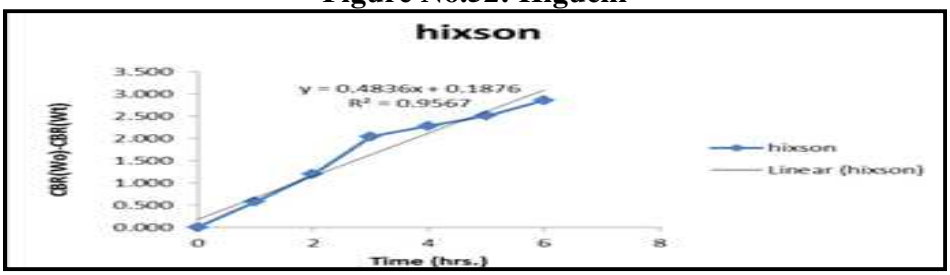


Figure No.53: Hixson

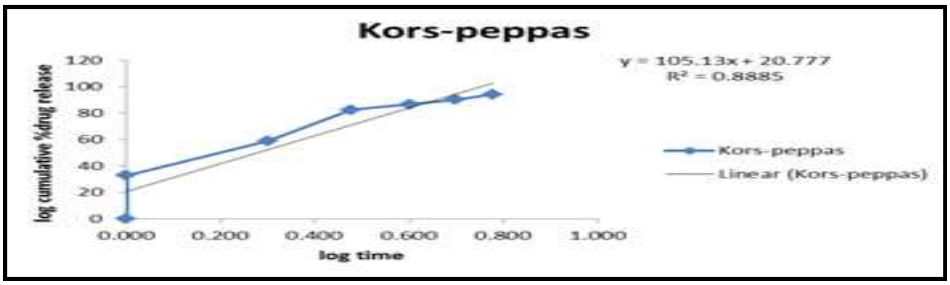


Figure No.54: Kors-Peppas

CONCLUSION

In this investigation microspheres were arranged effectively with dissolvable vanishing procedure. Microspheres would be positive for an oral medication conveyance framework having support medication discharge upto 12hrs. All the above plan was discovered equipped for medication ensnarement and with a decent rate yield. Associations are not seen in FTIR considers. Cyclobenzaprine Hydrochloride microspheres are a promising pharmaceutical measurement frames which give a continue medication discharge and staying away from the dosages reaction in the physiological districts. All the above definition, microspheres of F5 plan demonstrates 12hrs of more noteworthy medication discharge. The F5 formulae pursues zero request energy and fit into Korsemeyer-Peppas model. Cyclobenzaprine microspheres containing sodium alginate (F5) was effectively accomplished. The medication discharge was sustain upto12hrs with less portion dumping.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur, Uttar Pradesh, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Chien Yie W. Novel Drug Delivery System, Revised and Expanded, *Marcel Dekker, New York,* 2nd Edition, 1992, 648.
2. Michael Rathbone J, Jonathan Hadgraft, Michael Roberts S. Modified Release Drug Delivery Technology, *Marcell Dekker Inc, New York,* 2003, 943.
3. Gilbert Banker S and Rhodes Christopher T. Modern Pharmaceutics, *Marcel Dekker Inc, New York,* 3rd Edition, 1996, 943.
4. Salsa T, Veiga Francisco J B, Pina Maria Eugenia. Oral controlled-release dosage forms, I. cellulose ether polymers in hydrophilic matrices, *Drug Develop. Ind. Pharm,* 23(9), 1997, 929-938.
5. Jantez G M, Robinson J R, Banker G S, Rhodes C T. Sustained and Controlled Release Drug Delivery Systems, *Modern Pharmaceutics, Marcel Dekker Inc, New York,* 1996.
6. Popli Harinder, Sharma Shashank. Trends in oral sustained – Release formulations-I, *The Eastern Pharmacist,* 32, 1989, 99-103.
7. Lachman Leon, Lieberman Herbert A, Kanig Joseph L. The Theory and Practice of Industrial Pharmacy, *Varghese Publication,* 2nd Edition, 1986, 902.
8. Robinson J R, Lee V H K. Controlled Drug Delivery, Fundamental and Application, *Marcel Dekker, New York,* 29, 1987, 5-12.
9. Benoit J R, Marchais H, Rolland H, Velde V V. Methods and Industrial Applications, *Marcel Dekker, New York,* 1996.
10. Chinna Gangadhar B, Shyam Sunder R, Vimal Kumar Varma, Sleeva Raju M, Sai Kiran M. Formulation and evaluation of indomethacin microspheres using natural and synthetic polymers as controlled release

dosage forms, *International Journal of Drug Discovery,* 2(1), 2010, 8-16.

11. Luypaert J, Zhang M H, Massart D L. Feasibility study for the use of near infrared spectroscopy in the qualitative and quantitative analysis of green tea, Camellia sinensis (L.), *Analytica Chimica Acta,* 478(2), 2003, 303-312.
12. Subrahmanyam C V S. Micromeritics In: Text book of physical pharmaceutics, *Vallabh Prakashan, Delhi,* 2nd Edition, 2000, 180-234.
13. Vaghani Subhash, Vasanti S, Chaturvedi Kiran, Satish S C, Shankar S J. Formulation and Evaluation of 5-FU Loaded Eudragit Microspheres: Effect of Various Eudragit on Micromeretic Properties of Microspheres, *Journal of Macromolecular Science, Part A: Pure and Applied Chemistry,* 45(12), 2008, 1015-1027.
14. Pavia Donald L, Lampman Gary M, Kriz George S, Vyvyan J A M E S. Introduction to spectroscopy, *U.S.A,* 5th Edition, 2009, 784.
15. Thompson C J, Hansford D, Higgins S, Rostron C, Hutcheon, Munday D L. Evaluation of Ibuprofen-Loaded Microspheres Prepared From Novel Copolyesters, *International Journal Pharmaceutics,* 329(1-2), 2007, 53-61.
16. Sudhamani T, Kumar Reddy Noveen K, Kumar Ravi V R, Revathi R, Ganesan V. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery, *International Journal Pharmaceutics Research and Development,* 2(8), 2010, 119-125.
17. Das M K, Senapathi P C. Furosemide-loaded alginate microspheres prepared by ionic cross-linking technique: Morphology and release characteristics*, International Journal of Pharmaceutical Science,* 70(1), 2008, 77-84.
18. Das M K, Rao Rama K. Microencapsulation of Zidovudine by Double Emulsion Solvent Technique Using Ethylcellulose, *International Journal of Pharmaceutical Science,* 69(2), 2007, 244-250.
19. Sahoo Sunit Kumar, Mallick Abdul Arif, Barik B B, Senapati Prakash C H. Formulation and *in vitro* evaluation of eudragit microspheres of stavudine, *Tropical Journal of Pharmaceutical Research,* 4(1), 2005, 369-375.
20. The guidance on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products was published as Annex 2, *World Health Organization, (WHO) Technical Report Series,* 1, 2009, 953.
21. Longo W E, Iwata H, Lindheimer T A, Goldberg E P. Preparation of hydrophilic albumin microspheres using polymeric dispersing agents, *J. Pharm. Sci,* 71(12), 1982, 1323-1328.

Please cite this article in press as: Shweta Singh Gautam *et al.* Preparation of sustain release microspheres of cyclobenzaprine hydrochloride using various polymers, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 8(3), 2020, 251-278.