Formulation And Evaluation of Sustained Release Microspheres of Procyclidine Hidrochloride

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***Abstract*—Microspheres are multi particulate drug delivery systems that are designed to deliver drugs to a particular location at a fixed rate. Microspheres are free-flowing powders made up of biodegradable proteins or synthetic polymers with particle sizes ranging from 1 to 1000µm. The study shows the method of planning and measurement of microsphere parameters. Microspheres are complex, such as bioadhesive microspheres, polymeric microspheres, magnetic microspheres, floating microspheres, radioactive microspheres. Microspheres may be used in various fields such as cosmetics, oral drug delivery, target drug delivery, ophthalmic drug delivery, gene delivery, and others listed in the study. In this study the results of water uptake test, in - vitro dissolution and SEM have shown satisfactory results.In this article, the value of the microsphere is seen as a novel drug delivery carrier to achieve site-specific drug delivery was discussed.**

***Index Terms*—microspheres, In-vitro dissolution, polymer,microspheres,SEM**

I. INTRODUCTION

Oral routes popularity can be partly related to its ease of administration and the traditional idea that drugs are absorbed as effectively as routinely eaten food when taken orally. The development of a pharmaceutical product for oral delivery, regardless of its physical shape, requires optimizing the features of the dosage form within the limitations imposed by gastrointestinal physiology. Hence, it is crucial to possess a comprehensive comprehension of diverse fields such as gastrointestinal physiology, pharmacokinetics, pharmacodynamics, and formulation design in order to adopt a systematic approach towards the effective production of an oral pharmaceutical dosage form. The complexity of the disciplines involved in the design and optimization of a delivery system increases in proportion to its level of sophistication. For the effective development of an oral drug delivery system, a solid scientific foundation is necessary. This foundation relies on a comprehensive understanding of three key aspects:[1,2]

i) Physicochemical,pharmacokinetic and pharmacodynamics characteristics of the drug.
ii) The anatomic and physiologic characteristics of the GIT, and
iii) Physicochemical characteristics and the drug delivery mode of the dosageform to be designed.

Regular drug administration is important for drugs with shorter half- lives, which can result in decreased patient compliance.To address the aforementioned issues,different types of controlled release dosage forms are developed and modified to cater to the needs of patients. compliance increase through prolonged effect; adverse effect decreases by lowering peak plasma concentration.

A controlled release dosage form is designed to maintain a consistent amount of medicine in the plasma by releasing the drug at a predefined pace over a prolonged duration. Microspheres are utilized as carriers for drugs in order to achieve controlled release in innovative drug delivery systems. Microspheres are spherical structures that consist of a continuous phase of one or more polymers, in which drug particles are dispersed at either the molecular or macroscopic level. They can also be described as monolithic spheres or therapeutic agents distributed throughout a matrix in the form of a molecular "dispersion of particles". The particle size ranges from 1 to 1000 nanometers. Three In addition, existing slow-release oral dose forms, such as enteric coated/double-layer tablets that release the medicine over a period of 12-24 hours, still may not effectively distribute the drug throughout the body and may cause irritation in the gastrointestinal tract.[3,4]

Typesof Microspheres[5,6,7]

Bio-adhesive microspheres

Adhesion refers to the process of drug molecules adhering to a membrane by utilizing the adhesive properties of water-soluble polymers. Bio adhesion refers to the attachment of a medication delivery device to the mucosal membrane, such as the buccal, ocular, rectal, nasal, etc. These particular microspheres have a longer duration of staying at the location where they are applied, leading to close contact with the area of absorption and resulting in improved therapeutic effects.

A. Magnetic microspheres

This type of delivery method is crucial as it specifically targets the drug to the site of the sickness. In this scenario, a reduced quantity of magnetically targeted medicine can substitute for a larger quantity of drug that circulates freely. Magnetic carriers, such as chitosan and dextran,exhibit magnetic properties when exposed to a magnetic field due to the presence of integrated components in magnetic microspheres. The many types include:

A. Therapeutic magnetic microspheres: These are utilized for the targeted delivery of chemotherapeutic agents to liver tumors. This technique can also be used to target drugs such as proteins and peptides.
B. Diagnostic microspheres can be utilized for liver metastasis imaging and differentiating bowel loops from other abdominal structures. These microspheres consist of supramagnetic iron oxides, which create nano-sized particles.

B. Floating microspheres

In the liquid form, it is less dense than gastric juice, so the liquid remains in the stomach without affecting the rate of inflation. If the system runs on the stomach of the fetus and increases the presence of the stomach and increases the difference in plasma concentration, the drug is administered at the required speed. In addition, it reduces the risk of side effects and dosage availability. Another way is to make a long-term medicinal product that reduces the dosage frequency. The medicine (ketoprofen) is given in this form 8

C. Microradiation

The radio therapeutic microspheres are 10-30 nm larger than the capillaries and affect the firstbed depending on the effect. They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surroundingtissues.9 It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microsphers are α emitters, β emitters, γ emitters.10

Polymeric microspheres

The various types of polymer microorganism can be grouped as follows they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and naturally bio adhesive. Biodegradable polymers prolong the residence time when contact with mucous membrane due toit's high degree of swelling property with liquid medium, results gel formation. The rate and extent of drug release is controlled by concentration ofpolymer10 and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiencyofbiodegradablemicrospheresiscomplexand isdifficulttocontrolthe

Different Methods of Preparation of microspheres include:

1. Emulsion solvent evaporation technique
2. Emulsion crosslinking method
3. Co-acervation method
4. Spray drying technique
5. Emulsion-solvent diffusion technique
6. Multi-emulsion method
7. Ionization

Advantages[8]

1.Reliable means to deliver the drug to the,target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

2.Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.

3.Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.

4.The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.

5.Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing in tracellularly.

6.Blood flow determination: Relatively large microspheres (10-15 μm in diameter) are useful for regional blood flow studies in tissues and organs. In most cases the microspheres are injected at desired locations in the circulatory system and eventually lodge in the capillaries. The microspheres and fluorescent dyes they contain are first extracted from the tissue sample, and then fluorescence is quantitated on a spectro fluorometer or fluorescence microplate reader. Traditionally, this type of study has been carried out using radiolabelled microspheres; however fluorescent microspheres have been shown to be superior in chronic blood flow measurements.

Release Of Therapeutic Agents

Erosion of the polymer;

Diffusion of the drug particles through the matrix;

Dissolution of the drug in the surrounding medium.[7]

Applications[9]

1.Assay-Coated microspheres provide measuring tool in biology and drug research.

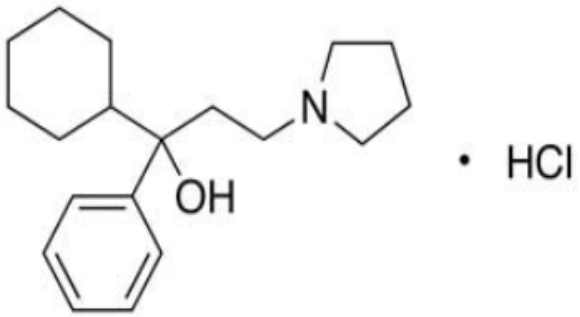
2.Buoyancy-Hollow microspheres are used to decrease material density in plastics (glass and polymer).

3.Ceramics-Used to create porous ceramics used for filters (microspheres melt out During firing, Polyethylene Microspheres)

4.Cosmetics-Opaque microspheres used to hide wrinkles and give color,Clear microspheres provide" smooth ball bearing" texture during application (Polyethylene Microspheres)

5.Electronicpaper-DualFunctionalmicrospheresusedinGyriconelectronic paper

TableNo.1:Drug Profile(Procyclidinehydrochloride)[10]

MolecularStructure	
IUPACName	1-cyclohexyl-1-phenyl-3-pyrrolidin-1-ylpropan-1-ol hydrochloride
MolecularFormula	$C_{19}H_{30}ClNO$
MolecularWeight	323.90
Bioavailability	75%
MeltingRange	85.5to86.5ºC
pKa	9.45
LogP	4.13
pH	5.0 to 6.5
Cmax	87.2 mcg/L
Tmax	1 to 1.3 h
Plasmahalflife	About6hr.
LOD	maximum 0.5%
Solubility	SparinglySolubleInWater,SolubleInEthanol (96%) PracticallySoluble InAcetoneAndEther
Description	WhiteCrystallinePowder,OdorlessorAlmost Odorless
Category	AnticholinergicAgent

Assay	98%To 101%OnDriedBasis
Moisture content	1.2%
Dose	Dailydosageusuallyranges10 to 30mgin divideddoses.

D. Parkinson'sDisease[11]

Parkinson's disease is a common, slowly progressive, neurodegenerative disease. It results from the degeneration of neurons in the substantia nigra, a region of the brain that controls movement. This degeneration results in a shortage of a neurotransmitter called dopamine, therefore, causing impaired movement. The first symptoms of the disease are usually seen later in life, 40 years or older. Parkinson's disease is often called primary parkinsonism or idiopathic Parkinson's Disease to distinguish it from other forms of parkinsonism.

Common Early Symptoms

- Tiredness
- Difficulty standing from a sitting position
- Shakiness Changes in speech
- Handwriting that looks cramped or "spidery"
- Losing track of words or thoughts
- Irritability and depression

II.METHOD

Formulation design of microspheres:[10,11]

TableNo2:1-Formulation design of microspheres

Sl no.	Ingredients	Formulationcode(Qty inmg)				
		F1	F2	F3	F4	F5
1	yclidinehydrochloride (mg)	100	100	100	100	100
2	SodiumAlginate(mg)	500	---	---	250	250
3	Carbopol934(mg)	---	500	---	250	---
4	SodiumCMC (mg)	---	---	500	---	250
5	CalciumChloride(gm)	7	7	7	7	7
6	AceticAcid(%V/V)	10	10	10	10	10
7	Water	q.s	q.s	q.s	q.s	q.s

TableNo-2:2- Formulation design of microspheres

Sl no.	Ingredients	Formulation code (Qty in mg)			
		F6	F7	F8	F9
1	yclidinehydrochloride (mg)	100	100	100	100
2	SodiumAlginate(mg)	----	200	150	150
3	Carbopol934(mg)	250	150	200	150
4	SodiumCMC (mg)	250	150	150	200
5	CalciumChloride(gm)	7	7	7	7
6	AceticAcid(%V/V)	10	10	10	10
7	Water	q.s	q.s	q.s	q.s

E. PreparationofMicrospheres:[12,12,14]

1.The polymer mixture was prepared by adding 20 ml of water to the amount of that polymer, and the total weight of the drug was dispersed in the polymer solution, and then the amount of sodium alginate, a polymer was also added to solution.

2.The obtained solution was poured in a 22G n idle syringe into different percentages of Cacl2 solution containing 10% V/V acetic acid.

3.The solution containing suspended grains was stirred for 2 hours with a red magnetic stirrer to improve the mechanical strength of the microorganism.

4.The fully formed beads were collected washed with ethanol and subsequentlydried at 400c for 12 hours.

III.EVALUATIONPARAMETERS:[15,16,17]

3.1. Water absorption Test:

Polymer swelling can be measured by the ability to absorb water and swelling. The study of water absorption in the microspheres was carried out using a USP dissolution apparatus.Chapter4ProcedureTPC40I.The microspheres are placed in a basket and rotated in a medium that has been diluted with 900ml of distilled water at a speed of 50rpm.Duringthe study, the environment was maintained at a temperature of 37±0.5 °C. After the selected areas, the package is dried to remove excess water and weighed. The swelling properties of the microspheres were expressed in terms of water absorption (WU). The values are given in table 5.10, the inflation pattern is shown in figure 4.1.WU (%) = (weight of swollen microbe – initial weight of microbe)/initial weight of microbe) X 100.

3.2. In-vitroDissolution Studies:

It is hoped that the drug will be delivered from various solid dosage forms (granules, tablets, capsules, etc.) that will still undergo molecular dissolution. This process is called elimination

A. Procedure:

Thereleasepropertiesofthemicrospheresunderlaboratoryconditionswereevaluatedusingarollingcurveanalyzer.500mLofwatermaintainedatatemperatureof37±0.5 °C was used as the production medium, and the package was rotated at a speed of 100 rpm. The amount of microspheres was weighed equal to 100 mg of the drug and placedinthepackages.Fewersampleswereretakenwhennecessary.Timelimitupto12hours for F1-F9 for Molations. The samples withdrawn were filtered, diluted suitably and analyzed at 262 nm spectrophotometrically for drug release.

Tolerances: The percentages of the labeled amount of $C_{19}H_{30}ClNO$ dissolved at the times specified conform to Acceptance Table 7.

Time(hours)	Amountdissolved
3	between20%and50%
6	between40%and70%
12	notlessthan 70%

TableNo3.1: Percentages of the labeled amount of $C_{19}H_{30}ClNO$ dissolved

Kinetic treatment: The data obtained from the in-vitro dissolution sudies was subjected for kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V_2 software.

Zeroorder kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$Q_t=Q_o+K_ot$

Where Q_t=amount of drug dissolved in time t.

Q_o =initial amount of the drug in the solution and K_o = zero order release constant.

First order kinetics:

To study the first order release rate kinetics the release rate data were fitted to the following equation,

Log $Q_t=\log Q_o+K_1t/2.303$(4.7)

Where Q_t is the amount of drug released in time t, Q_o is the initial amount of drug in the solution and K_1 is the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study their lease of water soluble and partially soluble or in soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$Qt=K_H \cdot t^{1/2}$

Where Q_t= amount of drug released in time t,

K_H=Higuchi dissolution constant.

Krosmeyer and Peppas release model:

Tostudythismodelthereleaseratedataarefittedtothefollowingequation, $Mt / M_{\square} = K \cdot t^{n}$

Where $Mt / M_{\square}$ is the fraction of drug release, K is the release constant, t is the release time and n is the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form.

3.3Scanning electron microscopy:

Procedure:

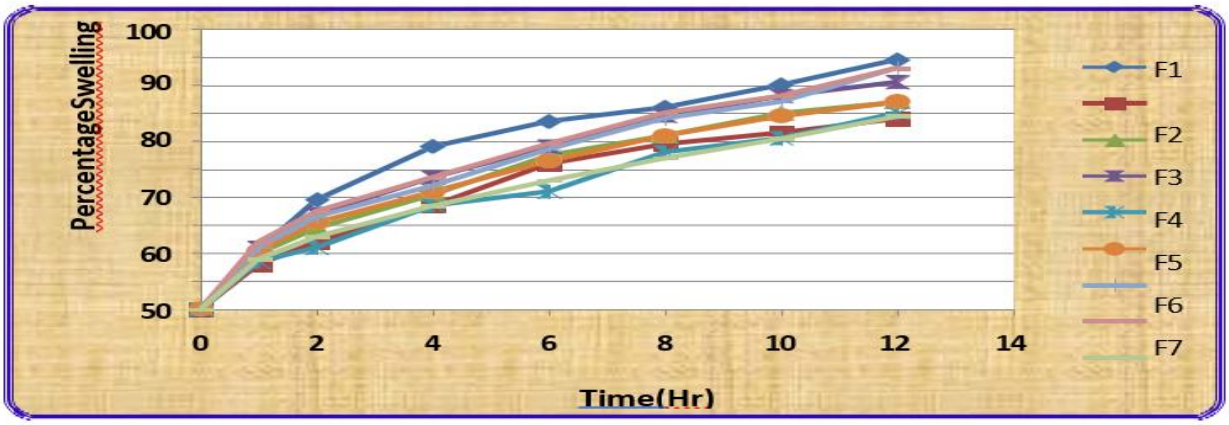
The outer morphology of the transdermal stitches looks over using a advanced microscope (JEOL, 6530 Tokyo, Japan). The sample is coated with gold palladium alloy and examine under the microscope.

IV.RESULT & DISCUSSION

4.1Water uptake test

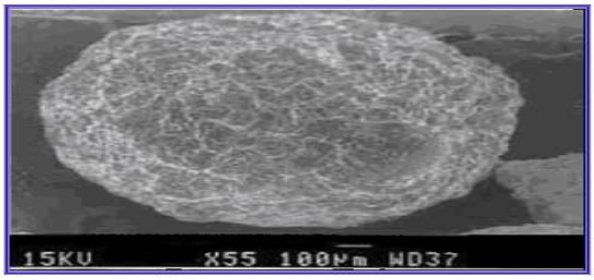
TableNo4.1: Water uptake test

ime Hr	PercentageSwelling								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21	16	20	22	17	21	22	24	18
2	39	24	29	34	22	31	33	35	26
4	58	37	41	47	37	42	44	47	37
6	67	52	55	58	42	53	57	59	46
8	72	59	62	69	56	62	68	70	54
10	80	63	70	76	61	69	74	76	61
12	89	68	74	81	70	74	86	86	69

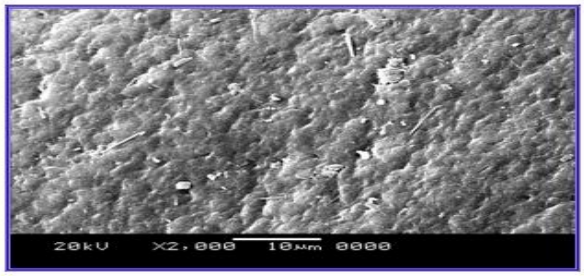


FigureNo.4.1: Water uptake test

ScanningElectron Microscopy(SEM) of Formulation(F2)

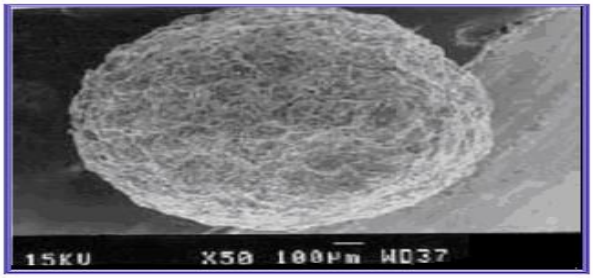


F-2: Under low magnification

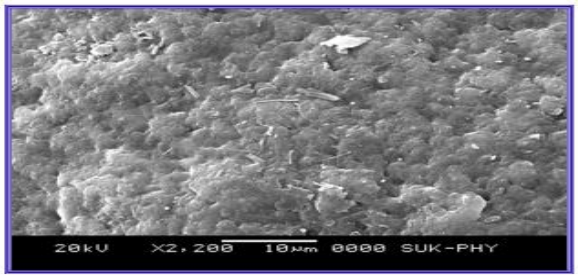


F-2: Under high magnification

Scanning Electron Microscopy (SEM) of Formulation (F9)



F-9: Under low magnification

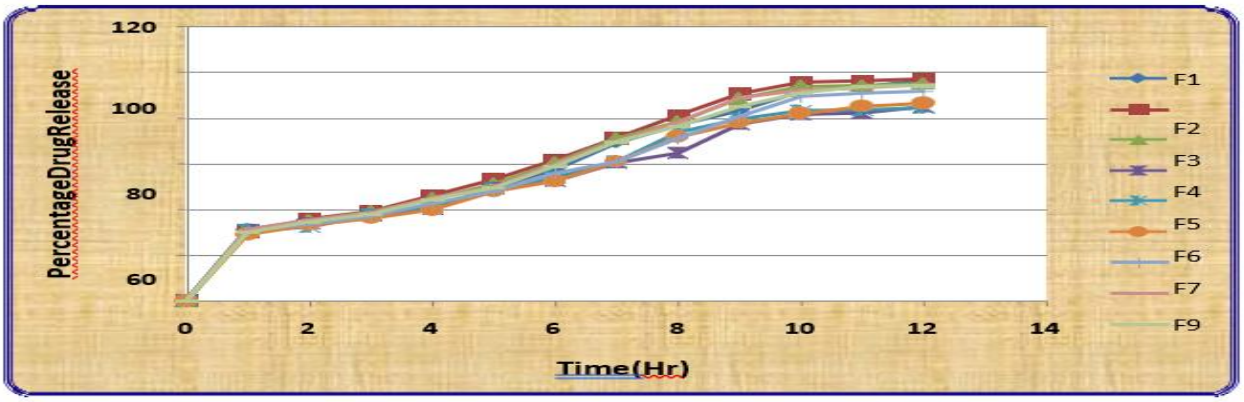


F-9: Under high magnification

FigureNo.4.2:Scanning Electron Microscopy(SEM) of Different Formulation

4.3Invitro Dissolution Profile;
Volumeofdissolutionmedium:500mlWater
Apparatus: USP-I (Basket)
Rotation Per Minute: 100 Procyclidinehydrochloride:100mg
VolumeWithdrawingForUVAnalysis:5ml
TableNo4.3:Cumulative % drug release of microspheres batches F1 toF9

Cumulative% drug release of microspheres batches F1to F9									
Time hr.	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	31.19	30.16	31.2	31	30.79	29.12	30.68	31.21	29.96
2	35.28	35.88	35.18	33.83	32.27	33.28	33.82	35.49	34.64
3	38.16	39.18	38.98	37.31	37.71	36.23	37.08	38.47	37.92
4	45	46.13	44.58	40.31	41.22	40.05	42.78	45.21	44.45
5	49.52	53.16	51.08	49.45	49.13	47.94	48	49.84	49.38
6	57.51	61.71	60.53	52.57	53.9	52.6	56.08	60.01	59.03
7	69.22	71.38	71.03	60.48	60.9	61.03	61.03	69.98	69.61
8	77	81.26	78.31	64.75	73.67	71.84	71.32	78.08	76.38
9	83.31	90.72	88.57	77.45	79.53	77.99	80.98	88.85	85.05
10	91.75	95.72	93.65	81.69	83.16	82.02	89.65	92.14	91.02
11	93.73	96.28	94.12	82.33	83.43	85.36	91.11	93.17	93.76
12	96.66	97.12	95.06	85.06	84.41	86.66	92	94.66	94.13



FigureNo.4.1: In-vitro Drug Dissolution for Proto type Formulation

Kinetics data of For Proto type Formulation
TableNo4.4: Kinetics data of Prototype Formulation

Formulation Code	Zero order	Firstorder	Higuchi	Hixon Crowel
	R^2	R^2	R^2	R^2
F1	0.945	0.939	0.979	0.969
F2	0.944	0.945	0.984	0.969
F3	0.939	0.952	0.983	0.97
F4	0.924	0.967	0.978	0.967
F5	0.926	0.965	0.979	0.965

F6	0.937	0.970	0.981	0.973
F7	0.939	0.957	0.978	0.968
F8	0.939	0.959	0.984	0.974
F9	0.944	0.962	0.985	0.975

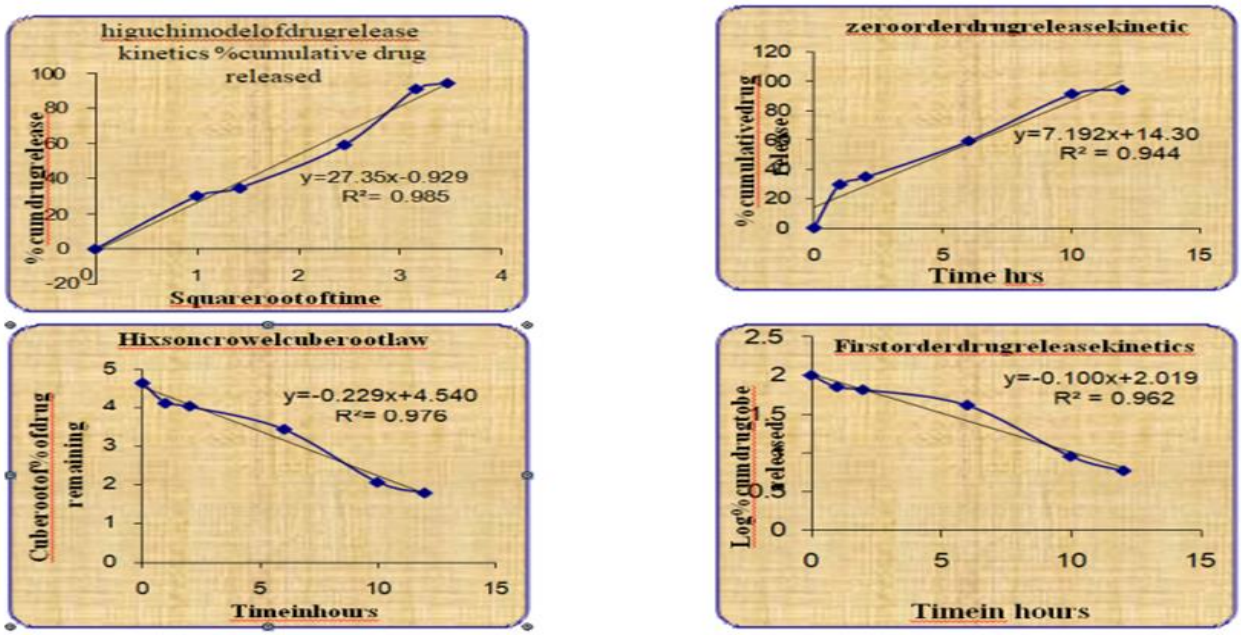


Figure4.2: drug release profile of F9 in various models

V. SUMMARYANDCONCLUSION

The goal of a drug delivery system is to deliver the right amount of drug to the right place in the body, including achieving and maintaining a drug concentration that needed. A microsphereis aprocess in which asolid shell surrounds or separates small solid particles or small liquid droplets. Procyclidine is used to treat the symptoms of Parkinson's disease or sudden movements caused by the side effects of certain psychiatric medications, a substance "1-cyclohexyl-1-phenyl-3-pyrrolidin-1-ylpropan -1-ol hydrochloride".The present study involves the micro production of procyclidine hydrochloride using sodium alginate, carbopol and sodium CMC with Cacl 2 and acetic acid reagent.Development and evaluation of microspheres with procyclidine hydrochloride as a drug model to increase drug delivery time. Attempts were made to prepare procyclidine hydrochloride microspheres using the ionization method, with the aim of releasing the drug in a stable or controlled manner into the digestive tract, thus to circulation system.

A review of the literature shows that a method has been used for the development of a micro-drug delivery system containing asthma, anti-hypertensive, NSAID and anti- diabetic drugs using ion technology.The polymers used in this method are carbopol and sodium CMC as a curing agent and sodium alginate as a transfer agent.In this study, four formulations were made using sodium alginate, carbopol and sodium CMC in different proportions.

All models were adjusted for various evaluation parameters like water uptake test, in - vitro dissolution, and SEM study have shown satisfactory results. The in vitro release study of formulations F1 to F2 and F3 to F4 shows a retarded release with increase in percentage of Sodium alginate, carbopol and Sodium CMC respectively. On the basis of release data and graphical analysis,formulation F2toF9showeda good controlled release profile up to 12 hours and F3 to F4 showed a good controlled release profile up to 12 hours.

The surface study of F2 and F9 viewed through SEM shows an uniform matrix formulation with dense nature and rough surface.

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