International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

"Preparation and Evaluation of Cepharadine Microbeads Containing Various Polymers"

Ganta Manasa , A.Bharani, B.vamsikrishna, A.Tulasikrishna Sk.Salmasulthana, N.Triveni, L.Madhuri, Dr.T.satyanarayana
Mother Teresa Pharmacy College, Sathupally, Khammam, Telangana

Submitted: 09-03-2023 Accepted: 18-03-2023

ABSTRACT :
The present research work discusses the formulation and evaluation of microbeads of Cephradine .Microparticulate drug delivery systems have various well known advantages over single unit dosage form . The microbeads were prepared by employing sodium alginate as a coating agent with HPMC as a release retardant and calcium chloride as a cross linking agent . Preparation of micro beads drug delivery system is one of the alternatives to over come which includes neither use of harsh chemical nor elevated temperature. The shape, size ,structure and surface characteristics were determined by scanning electroscope .The microbeads were found to be discreet and spherical in shape and had a smoother surface. The prepared microbeads were evaluated for various parameters.

Key words:HPMC, Micro particulate ,Scanning electroscope, Discreet, Cross linking agent

I. INTRODUCTION

Microbeads are uniform polymer particles, typically 0.5 to 1000 micrometres in diameter. Bio-reactive molecules can be adsorbed or coupled to their surface, and used to separate biological materials such as cells, proteins, or nucleic acids. Sodium alginate has been used as a matrix material to achieve controlled-release drug delivery due to its hydrogel-forming properties. Alginate salts are known to form a reticulated structure when in contact with calcium ions and their characteristic has been used to produce sustained release particulate systems for a variety of drugs. The ability of alginate sodium salt, to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry in sodium alginate's wide application as a carrier in hydrophilic matrix controlled release oral dosage forms .

DRUG SUITABLE FOR CONTROLLED OR EXTENDED RELEASE DOSAGE FORMS

Drugs having absorption window in stomach Drugs causing irritation and unsafe in the lower GI region. Highly active in stomach. Design of multi particulate drug delivery system is intended for oral, topical and parental formulation. Several multiparticulate includes pellets, granules, micro particles, lipoparticles, beads etc. These system consists of thousands of particles in which dosage form is substantially divided and embedded in which sub unit with selective diameter range. To achieve the desired therapeutic dose these sub units are encapsulated and compressed into tablet form. One of the multi particulate drug delivery system is hydrogel beads formulated from hydro collide polymers whose size ranges from 0.2 to 0.3mm and mostly spherical in shape.

ADVANTAGES

- Increased therapeutic efficiency as more drug reaches to target site.
- Avoid risk of toxicity.
- Plasma concentration of drug is maintained for prolonged period.
- Better absorption as surface area is increased.
- Patient compliance will be increased because of taste masking Improved stability.

DISADVANTAGES

- The main disadvantage are high cost and sensation felt by movement of the meggots.
- Hydrogels are non adherent, they made need to secured by a secondary dressing
- Incorporation of suitable concentrations of active ingredients for therapeutic uses in hydrogel beads are generally carried out by two methods.
- Incorporation of active ingredients during the process of preparation of hydrogel beads.
- Adsorption of a solution or suspension of active ingredients in previously cross linked hydrogel beads, when active ingredients are incompatible with dehydration solvents.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

- More preferable and more drug entrapment efficiently can be achieved by first process.

Preparation of hydrogel beads by using different techniques:

- Ionotropic gelation technique
- Emulsion internal Ionotropic gelation.
- Ionotropic gelation under a high voltage electrostatic field.
- Ionotropic gelation followed by coacervation.
- Multi polyelectrolyte hydrogel beads.

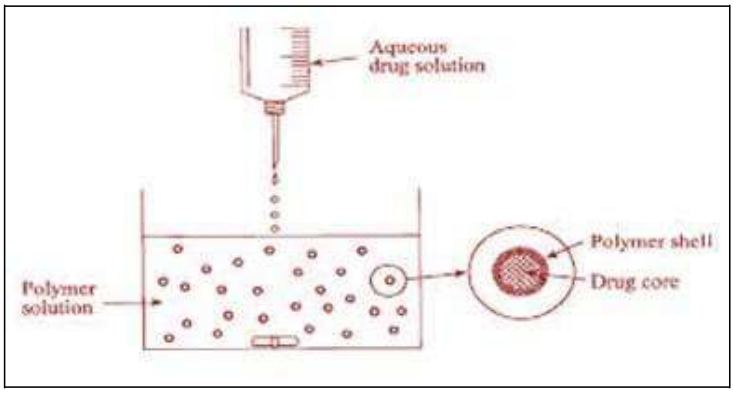
Techniques used for Formulation ofMicrobeads:
Ionotropic Gelation Method: It involves the interaction of an ionic polymer with oppositely charged ions to initiate crosslinking. Unlike simple monomeric ions, the interaction of polyanion with cations cannot be completely explained by the electro-neutrality principle. The three-dimensional structure and presence of other groups influence the ability of cations to conjugate with anionic functionalities or vice-versa. There are two submethods by which beads can be generated using ionotropic gelation technique. The methods differ from each other in the source of the crosslinking ion. In one of the methods, the cross-linker ion is positioned externally, whereas, in the other method, the cross-linker ion is incorporated within the polymer solution in an inactive form. occurs as a result of rapid diffusion of the cross-linker ions into the partially gelled beads

Ionotropic gelation methods classified into two types:

- External gelation method
- Internal gelation method.

External Gelation Method: The external gelation method involves the use of a metal ion solution as a source of the crosslinking ion. The polymer solution containing the drug is extruded through a needle into this solution with mild agitation. As soon as the polymeric drop comes in contact with the metal ion solution, instant gelation occurs, resulting into self-sustained bead formation. The beads are cured for a specified time period into the gelation medium following which, they are removed and dried. The external gelation

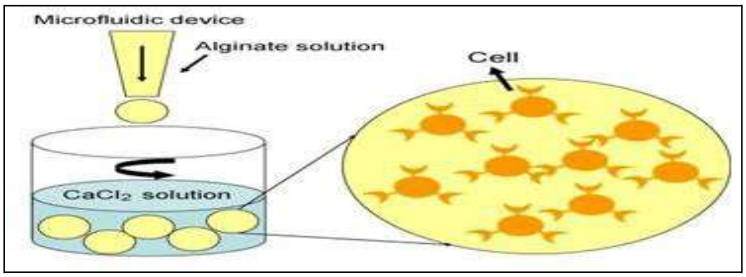
FIG. 01: EXTERNAL GELATION METHOD:



Internal Gelation Method: The internal gelation method involves the generation of the cross-linker ion ‘in situ’. This method involves the use of insoluble metal salt (such as calcium carbonate and barium carbonate) as a source of crosslinking cation. The cation is released, in-situ, by lowering the pH of the solution, thereby solubilizing the metal salt and releasing the metal ion

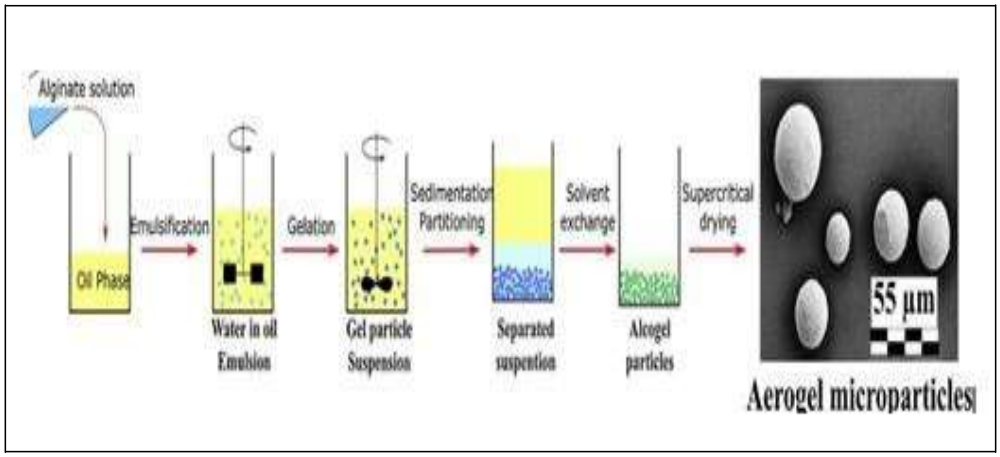
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

FIG. 02: INTERNAL GELATION METHOD :



Emulsion Gelation Method: Another method of microbead preparation is emulsion gelation techniques. The sodium alginate solution is prepared by dispersing the weighed quantity of sodium alginate in deionized water. An accurately weighed quantity of drug is added to the polymeric solution of Sodium alginate, and the drug is stirred magnetically with gentle heat to get a homogenous drug polymeric mixture. A specific volume of the crosslinking agent is added to form a viscous dispersion, which is then extruded through a syringe with a flat-tipped needle of size no. 23 into oil containing span 80 and 0.2% glacial acetic acid being kept under magnetic 100 stirring at 1500 rpm. The microbeads are retained in the oil for 30 min to produce rigid discrete particles. They are collected by decantation, and the products thus separated are washed with chloroform to remove the traces of oil. The microbeads are dried at 400 ºC for 12 h 18,

FIG. 03: EMULSION GELATION METHOD



Polyelectrolyte Complexation Method:

Another method of microbeads preparation is the complex coacervation of opposite Polyelectrolyte Complexation Method: Another method of microbeads preparation is the complex coacervation of oppositely charges polyelectrolytes, polycation, and polyanion materials. Alginate chitosan microcapsules with biocompatibility and biodegradability may be prepared under mild conditions. Even physiological conditions, so they are suitable for application in biomedical fields. In recent years, there has been an increasing interest in the study of the use of alginate– chitosan microcapsules as the drugdelivery systems of proteins and polypeptides. With this method, specific conditions of polyion concentration, pH and ionic strength, the mixture will separate into a dense concretive phase containing the microbeads and a dilute equilibrium phase. For example, complex coacervation between alginic acid and chitosan was achieved by spraying the sodium alginate solution into the chitosan solution, producing strong microbeads that remained stable over a large range of pH. For the best yield with coacervative bead preparation, conditions should be set to a pH of 3.9, ionic strength of 1 mm, and a 0.15% w/v total polyion concentration

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

II. MATERIALS AND METHODOLOGY

Preparation of drug loaded microbeads:TheCephradine microbeads were prepared by ionotropic external gelation technique. Sodium alginate (1-3%) was dissolved in deionized water at a temperature 45^0C using magnetic stirrer. On complete solution, an accurately weighed quantity of Cephradine was added and dispersed uniformly. The dispersion was sonicated for 30 minutes to remove any air bubbles formed during the stirring process. The bubbles free sodium alginate-drug dispersion (50 ml) was added drop wise through a 24-guage hypodermic needle fitted with 10 ml glass- syringe into 50 ml of calcium chloride solution (1-5%w/v) & isopropyl alcohol, stirred at 200 rpm for 30 minutes The droplets from the dispersion instantaneously gelled into discrete matrices on contact with the solution of calcium chloride&isopropyl alcohol . The drug loaded microbeads were further stirred in the solution of calcium chloride for an additional 0.5 - 2.5 hours. After the specified stirring time and stirring speed the gelled beads were separated by filtration, washed three times with deionized water, finally dried at 80 ^{0}C for 2 hours in a hot air oven.The dried microbeads were immediately preserved in air-tight containers.

Table 01:Composition and formulation variables of Cepharadine microbeads

INGREDIENTS	F1	F2	F3	F4	F5
DRUG	500	500	500	500	500
SODIUM ALGINATE	250	500	1000	750	250
CHITOSAN	-	-	-	250	250
HPMC	50	50	50	50	50
CALCIUM CHLORIDE(%W/V)	-	-	-	250	250
ISOPROPYL ALCOHOL	10	10	10	-	-
DRUG:POLYMER RATIO	1:1	1:2	1:3	1:4	1:1

Cephradine SA-Sodium alginate, all the formulations containing 500 mg of Cephradine Weight displayed is in mg,ml.

Evaluation of drug-loaded microbeads

Yield of microbeads:
The yield of formulated microbeads was evaluated by comparing the practical yield with that of the theoretical yield. The percentage of yield was calculated by using the following formula;

$$\text{Percentage of yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100 \quad (4.3.1)$$

Measurement of micromeritic properties of microbeads

i) Flow properties (angle of repose):

The flow characteristics of the drug loaded microbeads were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured..The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula;

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

Angle of repose[θ] =tan -1(h/r) ---------- (4.3.2)

H = cone height, r = radius of circular base formed by the microbeads on the ground.

Bulk densities: The bulk and tapped densities of the formulated granules or powder blendswere evaluated by using the bulk density apparatus. Known weights of microbeadswere transferred into a 50cc graduated measuring cylinder. Thecylinder was fixed on bulk density apparatus and the timer knob was set for 100 tapings. Then, the initialbulk volume and final volume after 50 tapings were noted. The experiment wasrepeated in triplicate. The respective densities calculated by using the following formulas;

$$\text{Bulk density [gm /cc]} = \frac{\text{Mass of the sample (g)}}{\text{Bulk volume (ml)}} \quad \text{---------- (4.3.3)}$$

$$\text{Tapped density [gm/cc]} = \frac{\text{Mass of the sample}}{\text{True volume}} \quad \text{---------- (4.3.4)}$$

Compressibility index or Carr's index value of microbeads was computed according to the following equation;

$$\text{Carr's index (CI \%)} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100 \quad \text{---------- (4.3.5)}$$

Hausner's ratio of microbeads was determined by comparing the tapped density to the bulk density by using the equation;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{---------- (4.3.6)}$$

Determination of particle size of drug loaded microbeads:

The average particle size of drug loaded microbeads was determined by optical microscopic technique. The Olympus model (SZX-12) having resolution of 30 xs was used for this purpose. Eyepiece of the microscope was fitted with a micrometer. The instrument was calibrated at 1unit of eyepiece micrometer equal to 1/30mm (33.33µm). Thirty microbeads were suspended in small quantity of liquid paraffin oil. The sample was spread over a clean glass slide placed on mechanical stage of the microscope. Estimate the size of each bead with the help of eyepiece. In all measurements at least 20 particles in five different fields were examined[140]. Each experiment was carried out in triplicate. The following formula is used to calculate themagnification value, mean particle size and standard deviation.

$$\text{Magnification value of EMM} = \frac{\text{No. of SMM divisions}}{\text{No. of EMM divisions}} \times 100 \quad \text{---------- (4.3.7)}$$

[Where, SMM = Stage micrometer; EMM= Eyepiece micrometer

Scanning electron microscopic analysis (SEM): The shape and surface characteristics were determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. Photographs were scanned within a range of 50-5000 magnifications

Estimation of drug content and drug entrapment efficiency:

Accurately weighed quantity of crushed Cephradine loaded microbeads were suspended in 100 ml of phosphate buffer containing 10 ml of methanol. The resulting solution was transferred into a stoppered conical flask and the flask was shaken for a period of 12 hours by using a mechanical shaker at room temperature. Next day it was stirred for 15 minutes. The solution was filtered, after suitable dilution; the drug content in the filtrate was analyzed at λ max 254 nm for Cephradine against a reagent blank prepared with dummy microbeads using UV-Visible spectrophotometer[142] (Shimadzu 1201). The obtained absorbance was plotted on the standard

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

curve to get the exact concentration of the entrapped drug. Each experiment was carried out in triplicate (n=3). The actual drug content and percentage of drug entrapment efficiency (DEE)

Determination of swelling properties of drug loaded microbeads:

The swelling properties of the drug loaded microbeads were determined in various pH ranges. Thirty uniform size dried microbeads were placed in small beakers containing 50 ml of pH 1.2 acidic buffer allowed to swell at 37^0C. After 2 hours interval, the equilibrium of swollen beads was observed and measured by Optical microscopy (Olympus model SZX-12). The magnitude of swelling was presented by the ratio of the mean diameter of swelling beads to the mean diameter of the dried beads before the test. Each experiment was carried out in triplicate (n=3). Swelling ratio was determinedfrom the following relation;

$$\text{Swelling ratio (\%)} = \frac{\text{Mean diameter at time (t) - Initial diameter (µm)}}{\text{Initial diameter (µm)}} \times 100 \quad \text{----4.3.12}$$

Weighed 50 mg of Cephradine loaded microbeads were placed in a small basket, soaked in pH 1.2, pH 4.8 and pH 6.8 buffer solutions and then shaken occasionally at room temperature. After a predetermined time to remove excess water, the swollen beads were immediately weighed on digital balance (GE-412 Sartorius).The experiment was performed in triplicate. The fresh samples were used for each individual time point. The percentage of weight gain by the samplecorresponding to swelling was calculated by using the formula.

$$\text{Swelling Index (\%)} = \frac{Wt - W0}{W_0} \times 100 \quad \text{----------} \quad (4.3.13)$$

Where; Wt is the weight of wetted microbeads at time (t) and W_0 is the initial weight of the microbeads at zero time (t)

In-vitro drug release studies:

The drug release studies were carried out using USP XIII rotating basket dissolution apparatus, (Model-TDT-08L, Electrolab Mumbai, India). The drug release profile from microbeads was examined in three different buffer solutions to mimic the various physiological regions of GI-tract. The drug loaded microbeads filled in empty hard gelatin capsule shells and put into the basket rotated at a constant speed 75 rpm and maintained temperature 37^0C. The 900 ml dissolution medium of pH 0.1N HCl was used for dissolution for 12 hours. Samples (5ml) were withdrawn at different time intervals over a period of 12 hours. After each sampling, equal volume of the medium was replaced with same volume of fresh medium. The sample was filtered through 0.45µ membrane filter and diluted with appropriate dilution with respective medium. Then estimate the cepharadineconcentration at λ max 254 nm

III. RESULTS AND DISCUSSION

The present study was aimed to developed Cephradine microbeads. All the formulations were evaluated for physicochemical properties, Invitro drug release and Stability studies.

Analytical Method:

Graphs Cephradine of was taken in Simulated Gastric fluid (pH 1.2) at 254nm.

Table 02:Observations for graph of cepharadinein 0.1N HCl (254nm)

Conc [µg/l]	Abs
0	0
5	0.163
10	0.314

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

15	0.438
20	0.563
25	0.719
30	0.813

Figure 04: Standard graph of cepharadine in 0.1N HCl

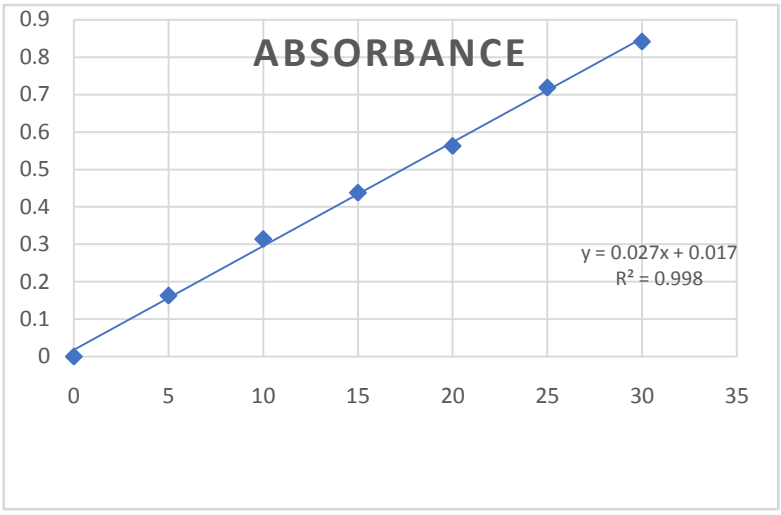
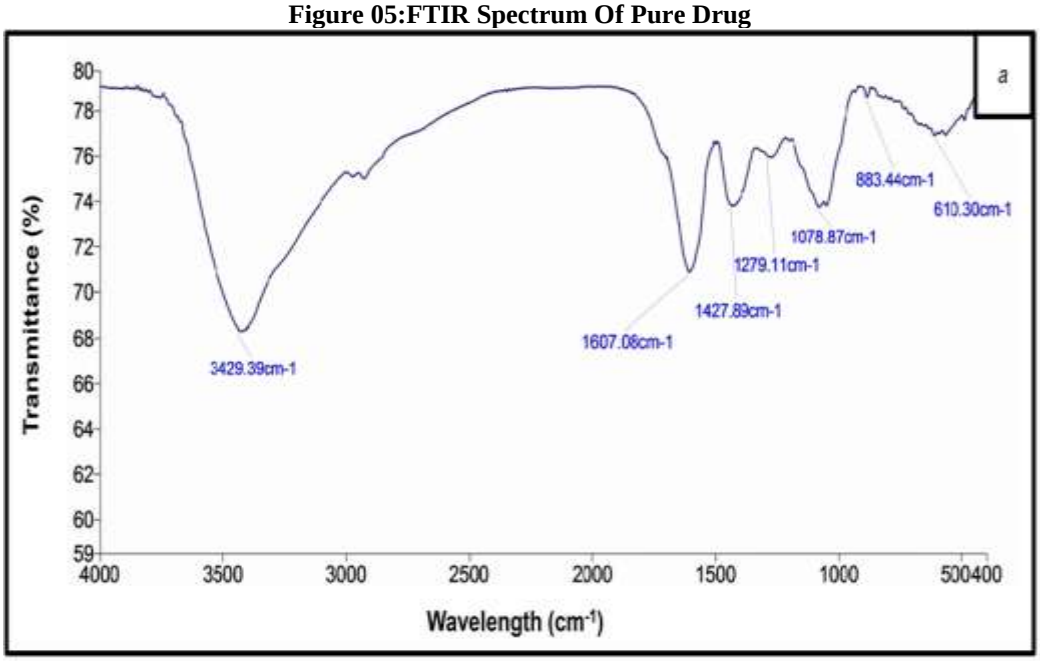


Figure 05:FTIR Spectrum Of Pure Drug



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

Figure 06:FTIR Spectrum Of Optimised Formulation Cephradine:

SEM RESULTS

Figure .07.optimized formulation

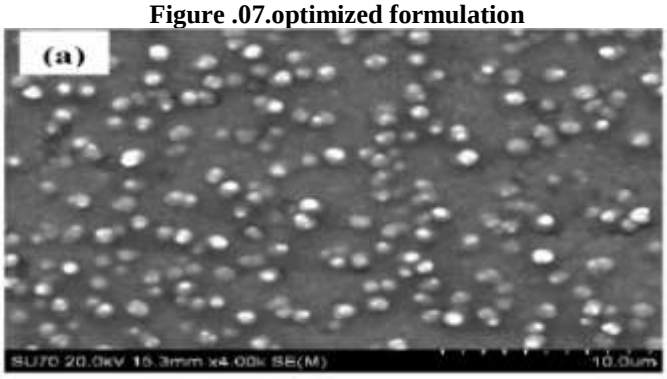
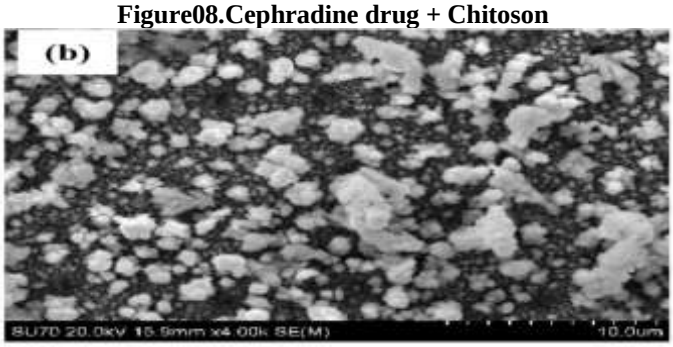


Figure08.Cephradine drug + Chitoson



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

Figure 09. Cephradine +sodium alginate:

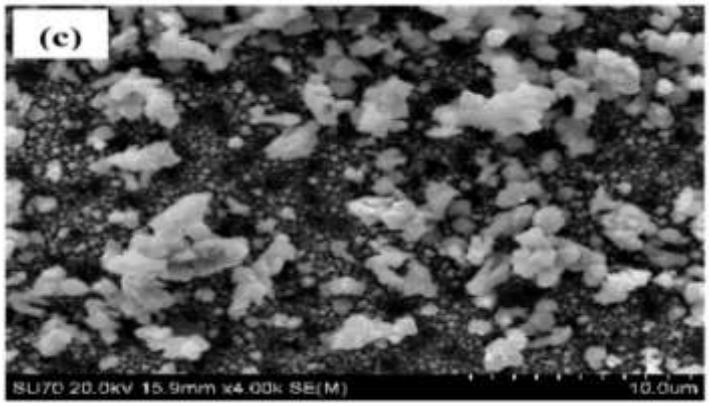


Table 03.Saturation solubility studies

S.NO	Sample	microbeads	Drug		Reading	
					Blank	Sample
1	F1	Sodium alginate	Cephradine	$0.H_2O$	0.000	0.440
2	F2	Chitosan	Cephradine	0.01N HCl	0.000	0.108
3	F3	HPMC	Cephradine	0.01N HCl	0.000	0.307
4	F4	Caragennine	Cephradine	$0.H_2O$	0.000	0.499
5	F5	SA+CH	Cephradine	$0.H_2O$	0.000	0.125

Table 04.rheological parameters of microbeads

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.01±0.02	0.48±0.05	0.56±0.07	15.21±0.05	0.86±0.02
F2	25.8±0.05	0.55±0.02	0.61±0.05	15.87±0.02	0.98±0.05
F3	28.74±0.07	0.51±0.09	0.65±0.02	17.11±0.05	0.64±0.07
F4	20.33±0.02	0.40±0.02	0.50±0.05	16.10±0.02	0.60±0.09
F5	25.24±0.09	0.43±0.05	0.61±0.02	17.92±0.07	1.2±0.02

n=3, Mean±SD values

Microbeads was subjected to various pre-formulation parameters. The angle of repose values indicates that the microbeads has good flow properties. The bulk density of all the formulations was found to be in the range of 0.40 to 0.55(gm/cm3) showing that the powder has good flow properties.The tapped density of all the formulations was found to be in the range of 0.50 to 0.61 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 15 to 17 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

Percentage yield:

Table 05.Percentage yield:

S.NO	Formulation code	Percentage yield
1	F1	90.5±0.07%
2	F2	88.5±0.08%
3	F3	83.5±0.06%
4	F4	94.75±0.05%
5	F5	92.5±0.03%

n=3, Mean±SDvaluesDrug content

Table 06:The drug content of the optimised microbeads was found to be

FORMULATION	F1	F2	F3	F4	F5
Actual Drug Content	89.95 ± 0.25	64.90 ± 0.78	69.54 ± 0.64	97.76±0.06%	67.87 ± 0.86
Drug Entrapment Efficiency	62.90 ± 0.78	89.95 ± 0.25	87.44 ± 0.90	96.96 ± 0.98	88.35 ± 0.93

n=3, Mean±SD values

Table 07: Swelling studies

Time (hrs)	F1	F2	F3	F4	F5
1	**1.09±0.02**	**0.87±0.05**	**0.80±0.07**	**0.68±0.02**	**0.72±0.05**
2	**1.28±0.05**	**1.16±0.02**	**1.14±0.05**	**1.12±0.08**	**0.96±0.09**
3	**2.92±0.08**	**2.48±0.07**	**1.72±0.02**	**1.63±0.05**	**1.66±0.02**
4	**3.18±0.07**	**3.55±0.08**	**1.77±0.09**	**1.82±0.02**	**1.98±0.05**
5	**4.78±0.09**	**3.33±0.09**	**2.58±0.08**	**2.32±0.09**	**2.57±0.07**

n=3, Mean±SD values

Table 08:Dissolution Data of cepharadine micro beads

TIME(hrs)	F1	F2	F3	F4	F5
0	0	0	0	**0**	0
1	29.02±0.02	28.04±0.05	18.87±0.02	**27.86±0.01**	27.73±0.06
2	43.32±0.05	41.65±0.02	35.66±0.05	**44.45±0.02**	42.04±0.01
3	55.28±0.01	53.81±0.05	51.06±0.02	**58.25±0.05**	64.33±0.02
4	66.08±0.06	64.53±0.02	63.63±0.01	**67.73±0.06**	83.84±0.05
5	70.44±0.05	69.43±0.01	69.71±0.05	**77.34±0.02**	84.32±0.08
6	80.9±0.02	79.98±0.05	79.27±0.02	**90.52±0.05**	89.44±0.02

n=3, Mean±SD values

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

Figure 10.Dissolution profile of CEPHRADINE microbeads (F1, F2, F3 formulations)

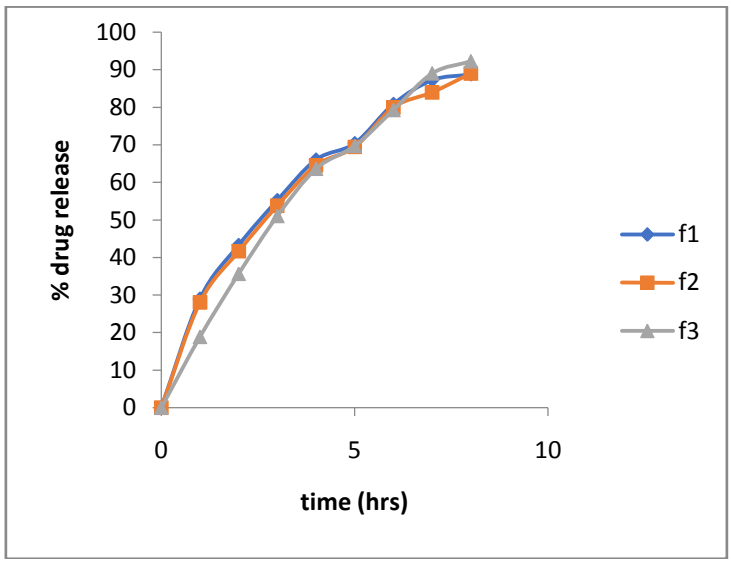
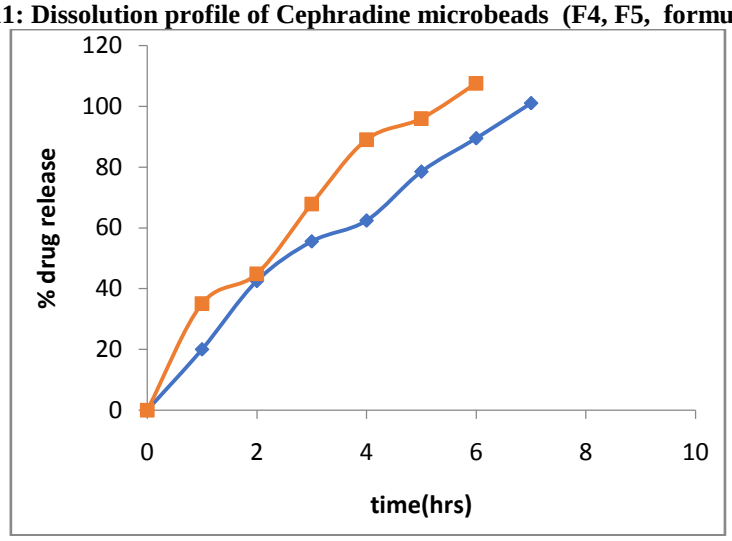


Figure 11: Dissolution profile of Cephradine microbeads (F4, F5, formulations).



Stability studies:

Table09.stability studies data for optimized formulation

S.no	Optimised formulation(F3) duration	25^0C(75%RH)	37^0C(75%RH)
1	1 MONTH	98.55%	98.10%
2	2 MONTH	98.27%	97.80%
3	3MONTH	98.20%	97.75%

n=3, Mean±SD values

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 235-246 www.ijprajournal.com ISSN: 2249-7781

By observing the stability studies it is concluded that the optimised formulation is stable through the entire period of 3 months and the drug release profile is also intact throughout the time being.

IV. CONCLUTION

- ✓ The objective of the present study is formulation and evaluation of Cepharadine microbeads to improve drug oral bioavailability.
- ✓ Cepharadine microbeads were prepared by ionotropic external gelatation technique using sodium alginate, Chitosan, caragennine in different ratios, various formulations were prepared with these polymers.
- ✓ The cepharadine microbeads were characterized with respect to IR, swelling studies, angle of repose, bulk density, tapped density, Carr's index Hauser's ratio, and stability studies and all the results indicated that the microbeads were having good flow nature.
- ✓ By the invitro dissolution studies it was concluded that the formulation (F4) was showing better result of 90.52% drug release.
- ✓ FTIR showed that there is no incompatibility between the drug and polymers.

REFERENCES

[1]. Shabaraya A R, Narayanacharyulu R.2003 "Design and Evaluation of Chitosan Microsphere of MetoprololTartarate for Sustained release". Indian. J. Pharm. Sci. 65(3):250-52.

[2]. Manjanna K.M, Shivakumar.B , Pramod Kumar T M.2009 "Natural polysaccharide hydrogel dexibuprofen microbeads for oral sustained drug deliver".J. Pharm. Res. Vol 2, No 7.

[3]. K.Naga R, Velmurugan S, B.Deepika B, Vinushitha S. 2011 "Formulation and InvitroEvaluation of Buccal Tablets of MetoprololTartrate". Int. J. Pharm. Pharm. Sci. Vol 3, Issue 2.

[4]. Sahoo S K, Mallick A A, Barik B B, Senapat P C.2005 "Formulation and in vitro Evaluation of Eudragit® Microspheres of Stavudine".Topical. J. Pharm. Res. June; 4(1): 369-75.

[5]. Patil J S, Kamalapur M V, Marapur S C, Kadam D V. 2010 "Ionotropic Gelation and Polyelectrolyte Complexation:The Novel Techniques To Design Hydrogel Particulate Sustained, Modulated Drug Delivery System". Digest. J. Nanomat. Biostruct. Vol. 5, No 1, p. 241 – 48.

[6]. Piyakulawat P , Praphairaksit N, Chantarasiri N, Muangsin N. 2007 "Preparation and Evaluation of Chitosan/Carrageenan Beads for Controlled Release of Sodium Diclofenac". AAPS. Pharm. Sci. Tech. 8 (4) Article 97.

[7]. Zhang Z-Q, Pan C-H, Chung D. 2011 "Tannic acid cross-linked gelatin–gum arabiccoacervate microspheres for sustained release of allyl isothiocyanate: Characterization and in vitro release study".Food. Res. Int. 44, 1000–7.

[8]. Mark D, Haeberle S, Zengerle R, Ducree J, Vladisavljevic G T. 2009 "Manufacture of chitosan microbeads using centrifugally driven flow of gel-forming solutions through a polymeric micronozzle". J. Colloid. Interface. Sci. 336, 634–41.