Formulation and Evaluation of Tailored Interpenetrating Polymeric Network (IPN) Beads of Trimetazidine Dihydrochloride for Controlled Drug Delivery

Madhuri H R *[1], Pradeep H K [2], Shankrayya.M [2], Pratiksha C C[3], Girish Bolakatti[4]

[1,2,,3] Department of Pharmaceutics, GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, India
[2] Department of Pharmaceutics, SCS College of Pharmacy, Harapanahalli, Karnataka, India
[4] Department of Chemistry, GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, India

***Abstract*-** Sodium carboxymethyl xanthan (SCMX) and sodium alginate (SAL) based microbeads loaded with Trimetazidine dihydrochloride were prepared by ionotropic gelation method using $CaCl_2$ as a cross-linking agent. The prepared microbeads were evaluated for % yield, size analysis, surface morphology, swelling behavior, drug release studies, *in vivo* antidepressant activity and stability studies of optimized formulation. The effect of different formulation variables like total polymer concentration, gelation time, concentration of cross-linking agent, and drug load on the extent of release was also examined.

***Index Terms*-** Microbead, Trimetazidine dihydrochlorides, Drug Release, Kinetics, Swelling.

I. INTRODUCTION

In the prevailing situation polymers are amongst the biggest volume chemical products in the world and the worldwide marketplace for polymer products is developing swiftly. Polymers have usually been precious excipients in tablet and tablet formulations [1]. In preceding periods, an ever-developing call for stepped forward polymer residences has paved the improvement of the blending of polymer combos.[2,3] In order to overcome the negative biological performance and to improve mechanical strength a new elegance of polymers has been delivered that are based totally on mixing of either herbal or synthetic polymers by myself or in mixtures. An interpenetrating polymer network (IPN) is defined as a blend of or greater polymers in a community with at least one of the systems synthesized inside the presence of another.[4] They also are one of a kind from graft copolymers and polymer complicated that contain both chemical bonds and/or low degree of cross-linking.[4] To gain most efficacy and minimal aspect outcomes it is important to supply the medication to goal website in optimal amount and for required time period.[5] Improved drug balance, greater the duration of therapeutic effect.[6]

II. MATERIALS AND METHODS

A gift sample of Trimetazidine Dihydchlorlide was obtained Yarrow Chem. Product Ltd. Mumbai. Xantan gum, Sodium alginate, Calcium Chloride, Monochloro acetic acid, and Glacial acetic acid from S.D. Fine Chem. Ltd., Mumbai, India. Other chemicals used were analytical grade.

a. Preparation of Sodium Carboxymethyl Xanthan gum (SCMX)[7]

Xanthan gum turned into derivatized to SCMXG the usage of following the technique suggested formerly. 2 gram of xanthan gum correctly weighed and dispersed in 6.7ml ice deionised water about 30 min which contains 3.024gm sodium hydroxide. Monochloroacetic acid (1.5 gm) turned into dissolved in deionised water, this become delivered to slowly for a length of one hour to the above mixture maintained at 15°to 18° C. Then the temperature of the aggregate changed into raised slowly to 60 to 65° C and stirred for at the least some other 1 hour. The wetted mass become washed with 20ml of 80% methanol three successive instances for approximately 15min. The pH of suspension turned into adjusted to impartial with glacial acetic acid. Finally, it changed into washed with methanol. The reaction aggregate became, then cooled to room temperature, cut into small pieces and dried at 50 to 60°C till to conjugative weight were the equal.

b. Preparation of blank IPN microbeads of SCMXG and SAL blend [8]

An aqueous solution of SCMXG and sodium alginate (SAL) combination hydrogel changed into organized and the pH of the solution turned into neutralized with acetic acid or sodium hydroxide. The resulting gum solution (pH 7.0) was introduced drop smart via a 21-gauge flat-tipped hypodermic needle into barely agitated one hundred ml of aqueous metal salt solutions containing 0.04% (w/v) Tween 80. Different metallic salt solutions having concentration of 4% (w/v) had been used in case of: $CaCl_2{\cdot}2H_2O$ and $AlCl_3{\cdot}6H_2O$ have been applied in two one-of-a-kind concentrations of 1 to2% w/v. Gelation of the hydrogel beads was performed at unique intervals of time. The capability of various salt answers to shape isolatable, self-status gelled beads become tested. The beads were formed straight away within the presence of trivalent Al_3^+ ions in each concentration. The beads had been, then remote with the aid of filtration, washed with double distilled water (2 × 100ml) and dried at 37°C in a warm air oven to consistent weight and stored in vacuum desiccators till used.

c. Preparation of drug loaded IPN microbeads of SCMXG and SAL blend

SCMXG-SAL mixture microbeads containing Trimetazidine dihydrochloride have been organized by way of single w/w emulsion gelation technique in a complete aqueous surrounding. Required amount of Trimetazidine dihydrochloride grow to be homogenously dispersed in an aqueous solution of SCMXG and SAL. The dispersion is added drop by drop by using 21 gauze flat tipped hypodermic needle into barely agitated 100ml of calcium chloride solution containing 0.04% w/w of tween 80. Followed by the process of filtration beads were separated and washed with distilled water twice and dried at 37° C in warm air oven and saved in vacuum desiccators.

FORMULATION DESIGN OF MICROPARTICLES

Micro particles were formulated by varying the %w/w of total polymer and the concentration of tween 80 is kept constant. The formulation of micro particles as shown in table no 1.

Table No. 1: Formulation of Microbeads

Sample code	SCMX%: SAL%	Drug load (% w/w of total polymer)	Gelation time (min)	Concentration of $CaCl_2$ (% w/v)	Tween 80 (% w/v)
F1	1:0.5	75	30	4	0.04
F2	1:1	100	30	4	0.04
F3	1.5:0.5	100	30	4	0.04
F4	1:0.5	75	30	5	0.04
F5	1:1	100	30	5	0.04
F6	1.5:0.5	100	30	5	0.04
F7	1:0.5	75	60	5	0.04
F8	1:1	100	60	5	0.04
F9	1.5:0.5	100	60	5	0.04

Compatibility studies

Compatibility studies were conducted using FTIR and DSC.

A. Fourier Transform Infra-Red Spectroscopy (FTIR)[9]

The drug-excipients interplay research has been achieved to test the physical and chemical interplay of materials that used inside the method. The drug excipients interaction turned into studied through FTIR spectroscopy via KBr pellet method. Sample for assessment and KBr were taken in 1:100 ratio and floor in motor for even distribution of pattern in KBr. The pellet turned into prepared inside the shape of disk with the aid of making use of pressure of 5 tons for 5min using hydraulic press and subjected to FTIR. The wave number range of 400-4000 cm^{-2}

B. Differential Scanning Calorimetry (DSC) Analysis[8]

Differential scanning calorimetry or DSC is a thermo analytical approach in which distinction in the amount of warmth required to increase the temperature of a sample and reference are measured as a function of temperature. Both the reference and the sample are maintained at the same temperature throughout the test. DSC (Perkin-Elmer thermal analysis) research have been executed as a manner to symbolize the physical state of drugs. Sample of natural drug and physical mixture have been positioned in the aluminium pans and thematically sealed. The heating temperature changed to 10° C in this step with min the use of nitrogen as herbal fuel. The DSC instrument changed into calibrated for temperature the usage of indium. In addition, the enthalpy calibration indium become sealed in aluminium pan with sealed empty pans as reference.

III. PHYSICO-CHEMICAL CHARACTERIZATION

Estimation of Percentage yield [11]

Percentage practical yield is calculated to recognize approximately percentage yield or efficiency of any technique; therefore, it facilitates in selection of suitable approach of production. Practical yield turned into calculated as the amount of microbeads obtained at the end of preparation and polymer and drug that are utilized in its preparation.

The percentage yield can be calculated by using formula % yield = (Practical Yield / Theoretical yield)* 100

Particle size determination [12]

Formation of microbeads and their shape have been studied the usage of a easy optical microscope method (Olympus, Tokyo, Japan). The length distribution records have been obtained using calibrated eye piece micrometer and average diameter become calculated. The microbeads have been dispersed in liquid paraffin and located under microscope, the diameters of 100 had been determined randomly.

The calculation of calibration can be accomplished as follows

$$1 \text{ eye piece division} = \frac{Number\ of\ Stage\ micrometer\ division}{Number\ of\ eye\ piece\ divisions}\ x\ Least\ count$$

Drug Entrapment Efficiency[13]

Drug entrapment efficiency of Trimetazidine dihydrochloride become determined by 10 mg equivalent weight of microbeads become beaten in a mortar pestle in appropriate buffers and it was kept for 24 hrs. Next day it was stirred for 15 minutes, and subjected for filtration. After suitable dilution, Trimetazidine dihydrochloride content material within the filtrate was analyzed by UV- spectrophotometer (Shimadzu 1800).

% Entrapment efficiency= (practical drug content/ theoretical drug content) ×100.

Swelling index[14]

Swelling behaviors of microbeads have been measured in both buffers (pH 1.2 and pH 7.4) solutions at room temperature and exactly weighed quantity of microbeads were allowed to swell for 24 hrs in given buffer which will make sure entire equilibrium. After that swollen bead have been eliminated and extra surface adhered liquid drops were removed through blotting and microbeads have been weighed via the usage of microbalance. The microbeads then dried in an oven till there was no trade in dried mass of pattern. The swelling index of the microbeads become calculated with the aid of the use of the formula

$$\text{Swelling index} = \frac{Mass\ of\ swollen\ microbeads - Mass\ of\ dry\ microbeads}{Mass\ of\ dried\ microbeads}\ X\ 100$$

Surface Morphology[15]

Scanning electron microscopy is used to decide surface topography, texture and to examine the morphology. SEM turned into performed by using the use of (JSM 6380 A JOEL, Japan). The sample of SEM had been organized by using lightly sprinkling the microbeads on a double adhesive tape which become stuck on aluminum stab. The stabs were then covered with gold to thickness about 300A the use of a sputter potter. The images had been taken by way of SEM analyzer.

***In-vitro release studies*[16]**

In-vitro drug release from the beads were studied in gastric media (pH 1.2, for preliminary 2 h) and intestinal (pH 7.4) situations using paddle type dissolution apparatus (Electro Lab TDT-08 Lumumba, India) organized with six baskets. Accurately weighed drug loaded dried beads equal to 50 mg drug have become located in 900 ml dissolution media maintained at 37 ± 0.50° C and the paddle emerge as circled at 50 rpm. At regular periods of time, a 5 ml pattern aliquot become withdrawn and the identical volume of sparkling medium turned into replenished immediately. The withdrawn aliquots were analyzed with the aid of UV spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan)

***Release kinetics*[17]**

Data acquired from in vitro release studies were suited for numerous kinetic equations consisting of zero order, first order, Higuchi version and Korsmeyer-Peppas model.

Zero order equation

$$Q = Q_0 - K_0 t$$

First order equation

$$\text{In } Q = \text{In } Q_0 - K_1 t$$

Higuchi equation

$$Q = K_2 t^{1/2}$$

Korsmeyer-Peppas equation

$$Q/Q_0 = K t^n$$

Where, K_0 to K_2 had been release rate constants Q/Q_0 was fraction of drug released at time t, K changed into a consistent and n become diffusion constant that shows widespread running release mechanism. For Fickian (diffusion controlled), $n \leq 0.5$; for non-Fickian (anomalous) release, 'n' value is in between 0.5 to 1.0; for zero order launch, n=1.0; for high-quality case shipping II, $n > 1.040$.

***Stability Studies*[18]**

Stability studies had been performed at 5^0C/ambient, 25^0C/60% RH and 40˚C/75% RH for three months using programmable environmental test chambers (Remi Instruments Ltd.)

IV. RESULTS AND DISCUSSION

Microbeads composed of SCMX and SAL have been prepared via ionotropic gelation process the use of $CaCl_2$ as a common cross-linking agent. In the present work, total 9 formulations were prepared and evaluated for IR and DSC study, scanning electron microscopy, drug entrapment efficiency, swelling index, *in-vitro* dissolution and stability study.

Drug - Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy

FTIR spectra of herbal drug showed the predominant peaks for N-H stretching at 3489-3565cm^{-1}, CH-CH stretching at 2984-3009 cm^{-1}, CH=CH at 1600-1500 cm^{-1}, Aromatic ring stretching at 1547cm^{-1}, N-H bending at 1504 cm^{-1}, and C-H bending vibrations at 1060 cm^{-1} that have been in comparison with the peaks of physical combination of drug with polymers. FTIR spectra evaluation found out no considerable interplay between diverse rational mixtures containing bodily aggregate of drug with polymers (i.e., SCMXG and sodium alginate) as shown in fig. 1, 2, 3, and 4**.** The FT-IR spectra of drug-polymer aggregate confirmed neither any shift inside the wave numbers of the peaks nor in the intensity, construed loss of interplay.

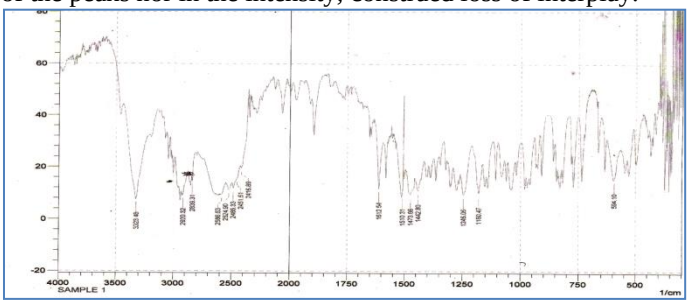


Fig no. 1: FT-IR Spectra of Trimetazidine Dihydrochloride

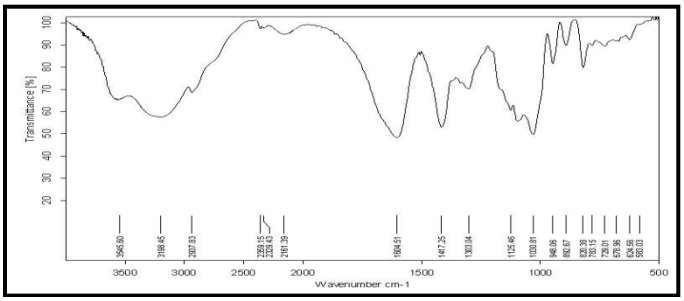


Fig no. 2: FT-IR Spectra of Sodium Alginate

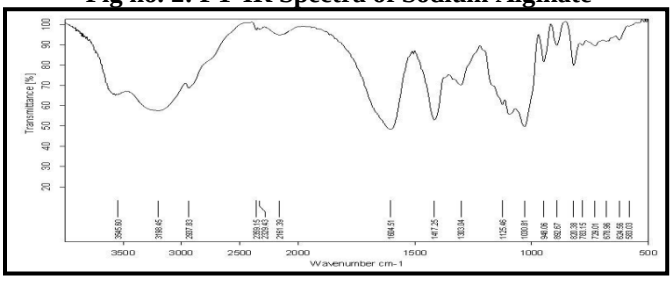


Fig no.3: FT-IR Spectra of SCMXG

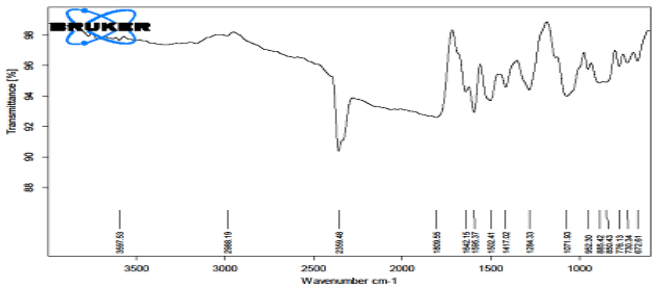


Fig no.4: FT-IR spectra of physical mixture of drug and polymers

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograms of natural Trimetazidine dihydrochloride and its physical mixture are shown in fig no 5 and 6. Pure Trimetazidine dihydrochloride confirmed a pointy endothermic at 242.67° C just like its melting point temperature. DSC thermograms of the physical combination confirmed a sharp endothermic top at 237.97° C and there may be no trade in the endothermic top of physical mixture in comparison to pure drug, this assertion further supported that the IR spectroscopic consequences which indicated the absence of any interaction among drug and excipient used within the formulations.

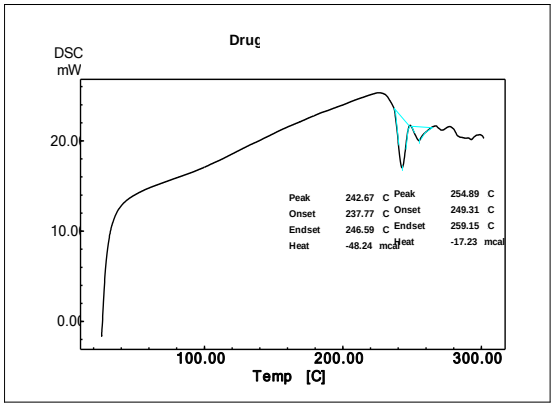


Fig no.5: Differential Scanning Calorimetry of pure Trimetazidine dihydrochloride

Table no: 2: Physicochemical drug evaluation parameters

Batch code	percentage yield (%)	Entrapment efficiency (%)	Swelling Index (%)
F-1	75.11	79.28± 0.88	40
F-2	78.33	87.1± 0.64	65
F-3	96.33	92.63± 0.12	75
F-4	88.8	78.63± 0.54	50
F-5	89	96.03± 0.32	70
F-6	91.3	98.1± 0.78	80
F-7	82	72.89± 0.22	40
F-8	88	73.42± 0.81	70
F-9	90.6	78.68± 1.02	85

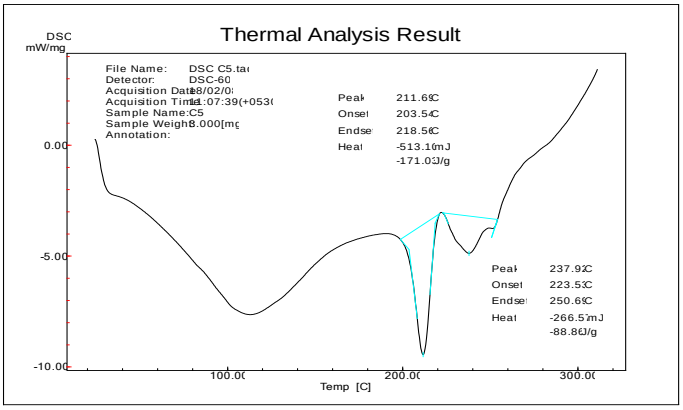


Fig no.6: Differential Scanning Calorimetry of physical mixture of drug and polymer

PHYSICO-CHEMICAL CHARACTERIZATION

Determination of percentage yield

The percentage yield of Trimetazidine dihydrochloride loaded beads become inside the variety from 62.5% to 95.6%and is shown in Table 2. From the effects it changed into determined that the proportion yield changed into various considerably through altering the ratio of SCMXG-SAL or by using increasing the concentration of cross-linking agent.

Entrapment efficiency:

Percent drug encapsulation efficiency increased with growing amount of SCMX and SAL ratio within the combination hydrogel network bead is confirmed in Table 2 for beads containing increasing ratio of SCMX and SAL from (0.5-1.5) %w/w at a fixed price of gelation time (30 min) to cross linking agent (4%), encapsulation performance had been increased from 90.00% to 98.00%.

Swelling Index

The release of a drug from a polymeric matrix is controlled through the swelling conduct of the polymer. To look at the impact of swelling of microbeads on drug launch, swelling ratio of beads was measured in phrases of water uptake at decided on time intervals. While the swelling ratio of the microbeads becomes very low in acidic answer, the identical property accelerated notably in alkaline answer (pH 7.4). The predominant functional institution presents in both the polymers that undergoes cross-linking with Cl^{2+} ions is –COOH group. In acidic solution, –COOH institution remains protonated and exerts insignificant electrostatic repulsive stress.

Particle Size Analysis

The result of particle size analysis is shown in Table 3. As the beads had been obtained through extruding the aqueous solution of combined polymers through a 21gauge flat tipped needle into cross linker solution, they exhibited a mono-modal and slender particle length distribution. Particles had been commonly located round in shape and the size was ranging from145 to 450 µm.s

Formulation Code	Average particle size (µm)
F1	216.35±6.51
F2	355.50±7.54
F3	403.62±11.39
F4	189.63±5.13
F5	237.77±4.89
F6	311.65±9.34
F7	134.09±6.43
F8	198.38±8.76
F9	267.77±14.83

Table no.3: Average particle size of Trimetazidine dihydrochloride microbeads (F_1 – F_9)

Scanning Electron Microscopy

The morphological assessment of the optimized microbeads system (SCMX and SAL) changed into accomplished by way of scanning electron microscopy (Figure-7a, 7b). SEM study found out that the microbeads have been nearly round in form with slightly tough floor and folded which became because of shrinkage of the beads at some point of the drying operation. The form of the beads was located to be greater round with stepped forward surface because the attention of $CaCl_2$ turned into improved from 4 to 5% w/v. This is because at low attention of the cross linker, more quantity of water is eliminated from the beads at some point of the drying manner which leads to the shrinkage of beads.

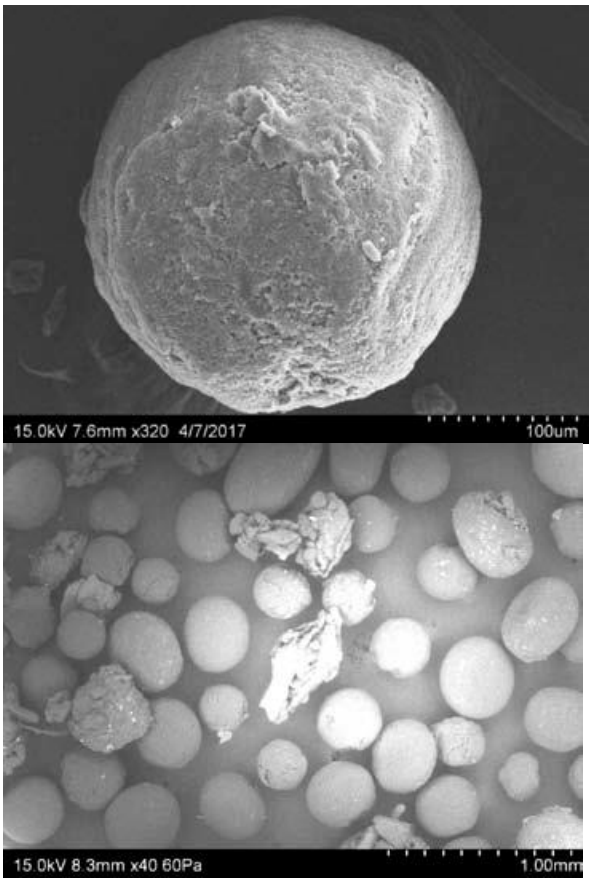
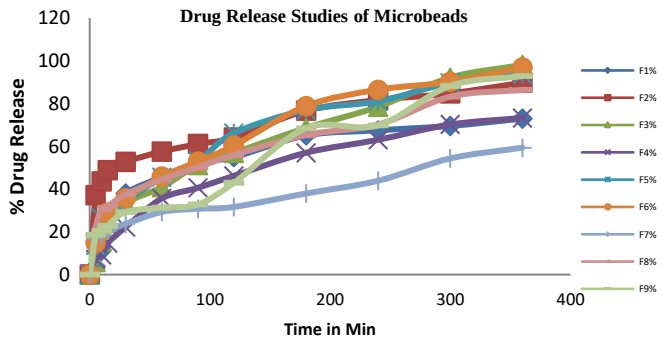


Fig. No 7a and 7b: SEM of Microbeads of formulation 5

In-vitro drug release study

In vitro drug release research has been finished in pH 1.2 and pH 7.4 and percent cumulative drug release as opposed to time records have been furnished in Fig. 8. The effect of the attention of crosslinking agent ($CaCl_2$) and gelation time on the release profiles of the drug was studied. The quantity of drug release in acidic medium (pH 1.2) turned into very low, however at pH 7.4, the amount of drug release improved considerably.

Fig. No 8: Drug release pattern of formulations



Stability studies

All the regulatory our bodies be given best actual time balance statistics for any drug or pharmaceutical for the cause of gaining access to shelf life and improved stability studies may additionally handily serve as device for method screening and stability trouble associated with shipping or storage at room temperature. On storage, the optimized microbeads (F6) did not show any change in physical properties and as well as no remarkable change in the drug content profile. At the end of 90 days, the optimized formulation (F6) was fairly stable at accelerated storage condition.

V. CONCLUSION

SCMX-SAL SCMX-SAL interpenetrating polymeric network beads changed into organized by ionotropic gelation method the use of Ca^{2+} ions as cross-linking agent for both the polymers. FTIR and DSC studies did now not screen any good-sized drug interaction. DEE of microbeads had been discovered to be moderately high (67.1 to 98.68%) and was now not laid low with formula variables besides the gelation time, as the increase of gelating time lower of DEE. The swelling studies of beads depicted an inverse dating of cross-linker concentration and gelation time with water uptake ability of microbeads. Further microbeads also displayed an extended-release profile in alkaline medium depending upon the method variables (polymer combination ratio, cross linker amount and gelation time). From the kinetic modeling of drug release facts was discovered that the formulations showed first order release kinetics, the mechanism of drug release from the microbeads observed non-Fickian kind transport mechanism.
Hence, we can conclude that high drug-loaded microbeads can be prepared using SCMX and SAL by means of ionotropic gelation technique and might be used to decrease the release of drug in acidic medium and to modulate the drug launch in alkaline solution (pH 7.4).

VI. REFERENCE

1. M. N. V. R. Kumar and N. Kumar, "Polymeric controlled drug-delivery systems: perspective issues and opportunities," Drug Development and Industrial Pharmacy, vol. 27, no. 1, pp. 1–30, 2001.
2. G. Blume and G. Cevc, "Liposomes for the sustained drug release in vivo," Biochimica et BiophysicaActa, vol. 1029, no. 1, pp. 91–97, 1990.
3. W. B. Liechty, D. R. Kryscio, B. V. Slaughter, and N. A. Peppas, "Polymers for drug delivery systems," Annual Reviewof Chemical and Biomolecular Engineering, vol. 1, pp. 149–173,2010.
4. P. Giusti, L. Lazzeri, and M. G. Cascone, "Bioartificial materials," in The Polymeric Materials Encyclopedia, J. C. Salomone, Ed., pp. 538–549, CRC Press, Boca Raton, Fla, USA, 1996.
5. Jain NK. Controlled and Novel Drug Delivery. 4th edn, 2001; pp. 236-237.
6. Sarmento B, Ribeiro AJ, Veiga F, Ferreira DC, Neufeld RJ. Insulin loaded nanoparticles are prepared by alginate ionotropic pre-gelation followed by chitosan polyelectrolyte complexation. J Nanosci Nano-technol 2007; 7; 2833-2841.
7. Wadher, K.J, Kakde R.B, and Umekar M.J. Formulation and evaluation of sustained release tablets of metformin hysdrochloride using hydrophilic synthetic and hydrophobic natural polymers. Indian J. Pharm. Sci., 2011, 73(2): 208-215.
8. Eunbi Cho, WonkyungCho, Kwang-HoCha, JunsungPark, Min-Soo Kim,Jeong-SooKim, HeeJunPark, Sung-JooHwang. Enhanced dissolution of megestrol acetatemicrocrystals prepared by antisolvent precipitation process using hydrophilicadditives. International Journal of Pharmaceutics 396 (2010) 91–98.
9. Dusel R., Sodium Alginate in 'Hand Book of Pharmaceutical Excipients,Published by American Pharmaceutical Association and the PharmaceuticalSociety of Great Britain, 1986; 257-258.
10. 'Sodium Alginate', Indian Pharmacopoeia, Ministry of Health and Welfare,Government of India, New Delhi, 1996; Vol. 2, 680
11. Eunbi Cho, WonkyungCho, Kwang-HoCha, JunsungPark, Min-Soo Kim,Jeong-SooKim, HeeJunPark, Sung-JooHwang. Enhanced dissolution of megestrol acetatemicrocrystals prepared by antisolvent precipitation process using hydrophilicadditives. International Journal of Pharmaceutics 396 (2010) 91–98.
12. Indian pharmacopoeia 2007, volume 1
13. British Pharmacopoeia Monographs: Medicinal and Pharmaceutical Substances: Venlafaxine Hydrochloride. 2009; 1 & 2.
14. Rajat Ray, Siddhartha Maity, Sanchita Mandal, Tapan K. Chatterjee, BiswanathSa. Development and Evaluation of a New Interpenetrating Network Bead ofSodium Carboxymethyl Xanthan and Sodium Alginate for Ibuprofen Release. Pharmacology & Pharmacy, 2010, 1, 9-17.
15. Thulasi V Menon, C.I.Sajeeth. Formulation and Evaluation of Sustained Release Sodium Alginate Microbeads of Carvedilol. International Journal of PharmTech Research. 2013. 5(2):746-753.
16. Yadav V D, Babar S A, Satheshkumar S, Shanmugasundaram P. Formulation and Evaluation of Floating Beads of Norfloxacin. IOSR Journal of Pharmacy. 2016, 6(9): 07-13.
17. Sherina V M, Santhi K and Sajeeth C I. Formulation and Evaluation of SodiumAlginate Microbeads as a Carrier for the Controlled Release of Nifedipine. International Journal of Pharmaceutical and Chemical Sciences. 2012. 1 (2); 699-710.
18. Kumaraswamy Santhi, Sokalingam Arumugam Dhanaraj, Abdul Nazer Ali, Mohamed Sherina. Formulation and Evaluation of Nifedipine Microbeads

Using Guargum as a Release Modifier. Int. J. Pharm.
Sci. Rev. Res., 2013, 21(1), 270-275.