International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.6, pp 1172-1184, 2017

Preparation and Characterization of sustained Release Ranolazine Microcapsules by W/O Emulsification-Solvent Evaporation Method

Kiran Thadkala[1], Mahender Reddy P[1], Jithan Aukunuru[1], Chintha Sailu[2]*

[1] Department of Pharmaceutics, Mother Teresa college of Pharmacy, Osmania University, Ghatkesar, Telangana, India
[2] Faculty of Pharmacy, University college of Technology, Osmania University, Hyderabad, Telangana India.

Abstract : Objective: The aim and objective of the present study is to prepare ranolazine sustained release microcapsules were successfully prepared using different ratios of polymers ethyl cellulose (EC) and hydroxy propyl methyl cellulose K4M (HPMC K4M) and tween-80 as emulsifying agent by w/o single emulsification-solvent evaporation method. **Materials and Methods:** Ranolazine is an anti-anginaldrug, it is given in the management of angina pectoris. On oral administration, this undergoes extensive first pass metabolism. Delivery of ranolazine microcapsules would minimize some of the deficiencies associated with the oral delivery, different batches of ranolazine loaded ethyl cellulose and HPMC K4M microcapsules were prepared to overcome the problem of low encapsulation efficiency of water soluble drug ranolazine, in different drug and polymers ratios using tween-80 as emulsifing agent and stabilizer with constant stirring by magnetic stirrer (Model-1 MLA, Remi motors, vasai, Mumbai, India) at 1500 rpm for 3 to 4 hours and centrifuged by cooling centrifuge (Hittich, Zentrifugen, model-1195 a, Mikro 220R, Germany) by w/o single emulsification-solvent evaporation method. The prepared microcapsules were evaluated and characterized for particle size, percentage yield, drug entrapment efficiency, surface morphology by scanning electron microscopy (SEM),drug-excipient compatibility studies byfourier transform infrared (FTIR), solid state properties (crystalline or amorphous) by differential scanning colorimetry (DSC), *in-vitro* drug release studies and release kinetics were determined. **Results:** It was observed that particle size decreased and was found to be in the range 220 to 350 µm, and highest percentage yield of 89.82% was shown, increased drug entrapment efficiency of 87% and increase in dissolution rate with sustained release property of drug with increase in concentration ratio of hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose were achieved. Based on the particle size, drug entrapment efficiency and in-vitro drug release data an optimized formulation having maximum drug release was selected. The optimized formulation F5 was characterized for particle size and surface morphology using optical microscopy method and scanning electron microscopy. The surfaceof the microcapsules were found to be wavy, smooth and spherical in micron size particles. FTIR studies indicated that polymers selected in the study are compatible with the drug, where there is no shift of drug peaks in the formulation. DSC studies indicated that the drug changed its physical structure in the presence of combination of polymers in the formulation F5.Ranolazinedrug release rate was observed highest with the increase in concentration of HPMC K4M and decreased particle size of microcapsules and showed sustained release property of drug by ethyl cellulose in pH 6.8 phosphate buffersup to 7 hrs.

From the formulation F1 to F8, F5 showed high dissolution rate.The percentage drug release of optimized formulation F5 was compared with the percentage drug release of pure drug. The data obtained from the dissolution profiles were compared for the different release kinetics models and the regression coefficients. The drug release profile follows zero order release and higuchi model kinetics; it was found that optimized formulation of ranolazine microcapsules showed sustained release property. All the results are reported.

Keywords : Ranolazine, hydroxyl propyl methyl cellulose, ethyl cellulose, tween-80, sustained release, microcapsule, single emulsification-solvent evaporation method, zero order release and higuchi model kinetics.

Introduction

The goal of any drug delivery system is to provid eatherapeutic amount of drug to the proper site in the body, to achieve promptly and then maintain the desired drug concentration. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. This results in a significant fluctuation in drug level (Chien YM., 1992). The concept of designing specified delivery system to achieve selective drug target in ghasbeen originated from the perception of Paul Ehrlich, who proposed drug deliveryto be asa "magicbullet". Sustained and novel delivery envisages optimized drug in the sense that the therapeutic efficacy of a drug is optimized, which also impliesnilor minimum side effects. The products may be more potentas wellas safer. Target specific do sage delivery is likely too vercome much of the criticism of conventional dosage forms. The cumulative outcome could be summarized as optimized drug delivery that encompasses great erpotency and greater effectiveness, lesser side effects and toxicity, better stability, low cost henc egreater accessibility, ease of administration and best patient compliance (Jain N K., 2001). The efficacy of a drug in a specific application requires the maintenance of appropriate drug blood level concentration during a prolonged period of time. However the conventional administration of drugs, gives a poor control of the concentration of these substances in plasma because of variations in the concentration of the bioactive product, once a specific dose has been administered. The conventional dosage systems can give rise to alternative periods of inefficacy or toxicity. These difficulties have been called for the development of new administration techniques for bioactive compounds, directed towards attaining the steady state plasma concentration. In the recent years, considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS). The reason for this paradigm shift is due to the low development cost and time required for developing a NDDS for the existing drugs rather developing a new drug molecule. In the form of NDDS, existing drug molecule can get a new life, thereby increasing the market value and product patent life [(1)]. Oral delivery of drugs is far by most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site-specific delivery, oral dosage forms have really progressed. In conventional dosage form, there is a little or no control over the drug release from the dosage forms, an effective concentration at the target site can be achieved by intermittent administration of drug, which results in constantly changing, unpredictable and often sub or supratherapeutic drug concentrations. Sustained release, prolonged action, extended release, depot dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Conventional pharmaceutical dosage forms give up drug to surrounding tissues or fluids at a time with varying rates that are highest initially and decline continuously. These include localized delivery of the drug to a particular part of body, drug stability, reduced need for follow up care and optimized drug absorption. Number of advances took place in the field of sustained drug delivery systems in the last few decades. During the preliminary stages of research on sustained drug delivery, major accent was focused on the development of zero-order devices. The primary objective of zero order release is to uphold constant drug concentration in blood for a prolonged period of time. Sustained release technology has emerged as an important new field in the development of pharmaceutical dosage form. Introduction of sustained release (SR) has given a new platform for NDDS, sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. More precisely, sustained drug delivery can be defined as a "sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable effects". The basic rationale of a sustained drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its unity is maximized through reduction in side effects and cure or control of condition in the

shortest possible time by using smallest quantity of drug, administered by the most possible route [(2)]. Successful fabrication of sustained release products is usually difficult as the following factors like consideration of physicochemical properties of drug, pharmacokinetic behaviour of drug, route of administration, disease state to be treated and most important is the placement of the drug in dosage form total which will provide the desired temporal and spatial delivery pattern for the drug such factors needs to be taken care. There are various approaches in NDDS and delivering a therapeutic substance to the target site in a sustained release fashion includes liposomes, microcapsules, microspheres, nanoparticles etc. Particulate delivery systems such as microcapsules and nanoparticles score over liposomes andas alternative to liposomes due the following technological limitations such as poor stability, low drug entrapment efficiency and greater cost of lipids. Drugs can be delivered to tumor in a sustained, continuous and predictable release fashion using polymers as delivery vehicles. Biodegradables polymers have been studies extensively over the past few decades to fabricate various novel drug delivery systems such as nanoparticles, microparticles and liposomes etc for sustained release property. The most accepted drug delivery system is the microparticulate drug delivery systems as they deliver the drug to the target site with specificity to maintain the desired concentration at the site of interest without adverse effects [(3)]. Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance. Microencapsulation has played a vital role in the development of sustained release drug delivery systems. Microcapsules have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and sustained drug release. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained. Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquid containing one or more drugs and dispersions [(4-5)]. Recently, the use of natural polymers in the design of drug delivery formulation has received much attention due to their excellent biocompatibility and biodegradability. Reasons for microencapsulation are sustained and prolonged release of drugs, masking of unacceptable taste or odour of drugs, preparation of free flowing powders from drugs in liquid form, stabilization of drugs sensitive to oxygen, moisture or light, elimination of incompatibilities among drugs, prevention of vaporization of volatile drugs, reduction of toxicity and to reduce gastro-intestinal irritation, alteration in site of absorption. Microencapsulation is a process of incorporating drugs into small size multi particulate units. A 'microcapsule' may be defined as a spherical particle with size varying from 1 to 1000μm containing a core substance. Microcapsules are mono or multinuclear materials embedded in spherical coating matrix are called microcapsules. It is a process by which solids, liquids or even gases may be enclosed in microscopic particles by formation of thin coatings of the wall materials around the substance. In addition, some related terms are used as well, for example, 'microbeads' and 'beads' alternatively. They differ from conventional hard or soft gelatin capsules in a number of important ways apart from size. They differ most notably in the greater variety of coating materials, in the comparative thinness of the coating formed, in their unique release properties and in their greater diversity of application in medicine. The core may also be referred as nucleus and the coating as wall or sheet. The concept of microcapsules dates to the 1930s and to the work ofBugerbergde jong and co-workers on the entrapment of the substances with in coacervates by national cash register company for the manufacture of carbonless copying paper. The usage of microsphere technology by pharmaceutical industry has been since 1960s.Depending upon manufacturing process various types of products are obtained in microencapsulation. These products are mono or multinuclear material enclosed by a coat or membranes are called as microcapsules. Since 1960, the technique of microencapsulation has been used in pharmaceutical industry. It is a process by which solids, liquids or even gases may be enclosed in microscopic particles by formation of thin coatings of the wall materials around the substance. The typical encapsulation process usually begins with dissolving the core material, in water. The material to be encapsulated is added and thoroughly dispersed by stirring. Then a solution of second material, which forms an insoluble complex is added. This additive material concentrates on the core material to form a film or coat around the particles of the substance to be encapsulated as a consequence of extremely low interfacial tension of the residual water or solvent in the core material so that a continuous film coating remains on the particle. The final dry microcapsules are free flowing discrete particles of coated material. Different rates of drug release may be obtained by changing the ratio of core to coating material, polymer used for coating and the method of microencapsulation [(6-7)].The uniqueness of Microencapsulation is the smallness of coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications. Although the active ingredient of many microencapsulated products can be varied from few per cent to over 99 per cent, the effectiveness of coating thickness that can be realized, regardless of the method of application employed varies from tenths of a micron to few hundred microns depending on the coat to core ratio, particle size and surface area of the core material, consequently the protective coatings that are applied are quiet thin. Ideal properties of

microcapsules are longer duration of action, control of content release, increase of therapeutic efficiency, protection of drug, reduction of toxicity, biocompatibility, sterilizability, relative stability, water solubility and dispersibility, bio-restorability, targetability, and polyvalent. The rate of drug release from microcapsules dictates their therapeutic action. Release is governed by the molecular structure of the drug and polymer, the resistance of the polymer to degradation, and the surface area and porosity of the microcapsules. Reservoir delivery systems extend the residence time of drug within the systemic circulation and were originally focused on zero-order dissolution kinetics [(8-9)].The advantages of microencapsulation are masking odour and taste of drugs, conversion of oil and other liquids into solids for the ease of handling, protecting of drugs from environmental conditions like moisture, heat, light and oxidation separation of incompatible materials (other drugs or excipients such as buffers), volatilization of encapsulated material can be delayed or prevented, improvement of flow properties of the powder, safe handling of substances and toxic substances, production of sustained release and targeted medication can be achieved, reduce dose dumping potential compared to large implantables, aid in dispersion of water insoluble substances in aqueous media. Apart from all the above mentioned advantages the phenomenon of microencapsulation has few limitations such as process conditions like change in temperature, pH, solvent addition, evaporation or agitation may affect the stability of core particles to be encapsulated and reproducibility is less and both the end products[(10)].Sustained drug release from microcapsules occurs by diffusion of drug through polymeric excipients, diffusion of entrapped drug as the polymer erodes, and release of drug through pores in the polymeric membrane. If the drug is released by diffusion through the polymer without erosion, the release depends on the surface area of the microcapsules and the path length followed by the drug in transit to the surrounding environment, for example, increasing the surface area by reducing particle size, results in an increased release rate. The path length of motion for the drug in the matrix can be sustained by manipulating the microcapsule loading; drug can be loaded by means of physical entrapment, chemical linkage and surface adsorption. Physicochemical properties of the drug and excipients such as permeability of one in the other, identity of the polymer, degree of crystallinity, inclusion of plasticizers and fillers, and thickness of the polymer, particle size influence the drug release rate. Before the process of microencapsulation a drug is required to be studied with respect to the following characteristics for successful fabrication and prolong release from the dosage form. Different types of methods are employed for the preparation of microcapsules given in table 1 [(11-12)].

Table: 1 Microencapsulation techniques with their relative particle size

S.No	Microencapsulation process	Relative particle size in µm
1	Air Suspension	35-5000
2	Coacervation-Phase seperation	2-5000
3	Co-extrusion	250-2500
4	Encapsulation by poly electrolyte multilayer	0.02 -20
5	Encapsulation by super critical fluid	0.5-1100
6	Fluid bed technology	20-1500
7	Hot melt	1-1000
8	Interfacial and In-situ polymerization	0.5-1000
9	Multi orifice centifugal	1-5000
10	Pan coating	600-5000
11	Phase inversion	0.5-5.0
12	Solvent evaporation	5-5000
13	Spinning disc	5-1500
14	Spray drying and spray congeling	600

Applications of microencapsulation:

This process of microencapsulation has been used medically for the encapsulation of live cells and vaccines, bio-compatibility of bio-molecules like proteins, peptides, harmones, artificial cells and various drugs were improved by encapsulating[(13-15)].

Materials and Methods

Ranolazine is a gift sample from Hetero drugs pvt limited, ethyl cellulose, HPMC K4M, tween-80, dichloromethane, methanol, n-hexane are from SD fine chemicals are AR grade. The preformulation studies with the ranolazine obtained were performed using conventional and reported techniques. The UV-Visible spectrum, solubility, flow properties, drug crystallinity were determined.

Preparation of Ranolazine loaded Ethyl cellulose-HPMC K4M Microcapsules:

Different batches of ranolazine loaded ethyl cellulose- HPMC K4M were prepared by w/o single emulsification-solvent evaporation method using tween-80 as emulsifying agent and stabilizer as give composition given in table 2, this method of preparation of microcapsules was reported to overcome the problem of low encapsulation efficiency of water soluble drug. Required quantity of ranolazine drug is dissolved in distilled water with tween-80 as aqueous phase and polymer (Ethyl cellulose: HPMC K4M) is dissolved in organic phase dichloromethane. To this organic phase, aqueous drug solution is emulsified under magnetic stirrerfor one hour with constant strring to prepare w/o primary emulsion. This primary emulsion is injected with butterfly microsyringe to the external aqueous phase containing cross linking agent calcium chloride with constant stirring by magnetic stirrer for (Model-1 MLA, Remi motors, vasai, Mumbai, India) at 1500 rpm for 3 to 4 hours. The prepared microcapsules were collected by centrifugation, filtered and then dried. The dried microcapsules are hardened by n-hexane and subjected for characterization and different evaluation studies[16-19].

Table: 2 Composition of Ranolazine Microcapsules:

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Ranolazine(mg)	100	100	100	100	100	100	100	100
2	Ethyl cellulose(mg)	1000	1000	1000	1000	1000	1000	1000	1000
3	HPMC k4M(mg)	250	500	750	1000	1500	1000	750	500
4	Tween 80 (ml)	0.25	0.25	0.50	0.50	0.75	0.75	1	1
5	Dichloromethane(ml)	10	10	10	10	10	10	10	10
6	Distilled water(ml)	5	5	5	5	5	5	5	5
7	% Calcium chloride solution in ml	15	15	15	15	15	15	15	15
8	Aqueous: Organic phase	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2

Preformulation studies as investigation of physical and chemical properties of drug substance alone or in combination with other excipient, which could affect drug performance and development of an efficacious dosage form. It acts as a foundation for developing good formulations and successful commercial products, to increase drug stability, to improve drug bioavailability, to reduce drug-excipient incompatibility and to determine its kinetic rate profile.

Characterization and Evaluation of Ranolazine Microcapsules:[20-24].

Particle size analysis:

The mean particle size was determined using optical microscopy method. In this method, the sizes of 250 particles were determined and the average particle size was calculated. Optical microscope can detect particles of sizes in micron with accuracy. If particles produced are in this size range, this technique can be conveniently used to measure the particle size and determinationof average particle size of ranolazine microcapsules withoptical microscopy, average size of microcapsules is reported.

Percentage yield:

To determine the yield, the weight of microcapsules obtained at the end of preparation was determined. The total weight of raw materials used to obtain this microcapsules was determined to obtain the theoretical yield.

Percentage yield was then determined using the formula:

Percentage yield = (Practical yield/theoretical yield) x 100

Drug entrapment efficiency (EE):

The amount of drug entrapped was estimated by dissolving the 100 mg of microcapsules in dichloromethane and water in 3:1 ratio under vigorous shaking for 1hour, the resultant solution is centrifuged both layers were separated and the soluble ranolazine in water was determined. The drug content in aqueous solution was analyzedspectrophotometrically by using UV-VIS spectrophotometer at 272.7nm with further dilutions against appropriate blank. The amount of the drug entrapped in the microcapsules was calculated using the formula:

$$\textbf{Drug entrapment efficiency (\%)} = \frac{\textbf{Amount of drug actually present}}{\textbf{Theoretical drug load expected}} \times 100$$

Scanning electron microscopy:

In order to examine the surface morphology shape and size of the particle scanning electron microscopy (SEM) was used. A concentrated aqueous suspension was spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with gold layer 20 nm thick. Photographs were taken using a scanning electron microscope (Hitachi, S-3700N, Tokyo, Japan) operated at 20 kV. The smallest size microcapsules were used for determining surface morphology.

Drug-excipient compatibility studies (FTIR studies):

FTIR spectrum of drug, polymer and physical mixture of drug with polymers and optimized formulation were obtained on FTIR instrument. Sample about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 Psi for 3 minutes. The resultant disc was mounted in a suitable holder in IR spectrophotometer (Shimadzu 8400S, Tokyo, Japan) and the spectrum was scanned over the wave number range of 4000-400 cm-1 in a scan time of 12 minutes. IR helps to confirm the identity of the drug and to detect the interaction of the drug with the carriers.

Differential scanning calorimetry (DSC):

DSC studies were performed to understand the nature of the encapsulated drug in the polymer and the physical state of drug in the polymer matrix would also influence its release characteristics. To probe this effect, DSC analysis was performed. Thermal analysis and properties of the powder samples (Ranolazineand optimized microcapsules) were investigated with a DSC (Shimadzu DSC 60, Tokyo, Japan). Approximately 10 mg of sample was analyzed in an open aluminum pan, and heated at scanning rate of 10°C/min between 0°C and 400°C under nitrogen atmosphere. Magnesia was used as the standard reference material to identify physical changes of drug in the formulation. Hence, it indicates the physical nature of drug is changed in the formulation from crystalline to amorphous.

***In-vitro* drug release:**

*In-vitro*dissolution studies of samples were carried out using USP XIV (Electro lab TDT-082, Model-ETC 11L, Mumbai, India) apparatus II paddle method by dispersed powder technique. Accurately weighed samples were added to 900 ml of buffer media 6.8 phosphate buffer at 37 ± 0.5°C and stirred at 100 rpm. An aliquot of 10ml was withdrawn at different time intervals up to 7 hours. The solid particles were prevented from pipetting by withdrawing the sample through a pipette fitted with a cotton plug. An equal volume of fresh dissolution medium was immediately replaced. The filtered samples were assayed spectrophotometrically at 272.7 nm respectively for ranolazine drug. The dissolution of microcapsules were compared with the dissolution of equivalent amount of the pure drug ranolazine and identified the sustained release property.

Drug release kinetics (Harris shoaib et al., 2006):

The obtained dissolution data was fitted into mathematical equation for zero order, first order, highuchi model and korsemeyer equation/ peppa's model in order to describe the kinetics and mechanism of drug release from the microcapsules formulations. To analyze the *in-vitro* release data various kinetic models were use to describetherelease kinetics.The zeroorder describesthesystemswhere thedrugreleaserateis independent ofits concentration. Thefirst order d escribes therelease from system whererelease rateis concentration dependent. Higuchi(1963)describedthereleaseofdrugsfrominsolublematrixasasquareroot oftime dependent process based on fiction diffusion.

Results and Discussion

Preformulation studies for ranolazine has been performed to know the drug physical properties so as to design it to suitable formulation. It is white amorphous and freely soluble in water and wave length maxium of 272 nm. Percentage yield was found to be 89.82, highest for F5 formulation and least for F1 formulation. From the results of drug entrapment efficiencyit can be concluded that there is a proper distribution of ranolazine in the microcapsules. The drug entrapment efficiency was found to be 75% to 87%, and a maximum of 87% drug entrapment was found to be for F5. Particle size was found to be 320µm for F1 formulation and in the subsequent formulations the particle size was found to be decreased this is because of increase in concentration of polymers and emulsifying agent, surface area of the microcapsules increases and thereby particle size decreases and found be small for F5 with 220 µm, the range is 220 to 350µm.Surface morphology of the microcapsules was examined by scanning electron microscopy, the optimized microcapsule formulation F5 was examined for SEM analysis. Microcapsules were smooth, wavy, spherical, free flowing in nature and were obtained in the micro range between 19.5 to 271.5 µm as shown fig 1 and 2.From the below fig 3, 4 and 5 FTIR spectra of pure drug, physical mixture and optimized formulation F5, it was observed that all characteristic peaks of ranolazine were present in the combination spectrum and there is no shift in peaks, thus indicating compatibility of the ranolazine with polymers where there is no physical and chemical interaction of drug and polymers.Thus it confirms drug and excipients are compatible.The physical state of ranolazine in the polymer would also influence the release characteristics of drug it was determined by DSC studies. To probe this effect, DSC analysis was performed on ranolazine and optimized microcapsules F5.From the DSC thermograms below fig 6 and 7, it was observed that characteristic thermogram of drug at 125 ^{0}C, but in thermograms of physical mixture, solid dispersion and optimized formuation F5 the thermogram disaapeared at 125 ^{0}C and thermogram shown at 250 ^{0}C. Hence it indicates the physical nature of drug is changed in the formulation, the amorphous form of drug is changed to crystalline form DSC results. The dissolution was carried out for a period of 7hrs in 6.8 pH phosphate buffer. The cumulative percent release of F 1to F8 formulations at various time intervals was calculated and tabulated in table 3. The graph plotted between cumulative percent drug release in all formulations against time shown in fig 8. The Maximum percent of drug release was found in F5 formulation which contains 93.68% maximum drug entrapment. The formulations followed the zero order for the drug release study with higuchi's model thus they indicate diffusion mechanism. The peppa's plot showed the n value of 0.9395 for formulation F5, thus indicating non- fickian diffusion. Thus prepared ranolazine microencapsules shows sustained release system.

Table: 03 *In-vitro* cumulative % drug release data of Ranolazine microcapsules

Time in hr	**% Cumulative drug release**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	11.6	13.6	10.88	12.73	16.7	15.4	14.9	15.6
2	35.2	44.3	38.5	40.2	49.5	38.5	42.6	41.2
3	55.4	59.2	60.1	60.9	63.2	61.2	57.5	58.2
4	72.4	74.3	75.3	76.8	81.27	77.2	74.8	70.8
5	74.6	76.3	78.9	79.8	83.27	79.5	76.8	73.4
6	75.6	77.1	80.93	80.5	87.27	81.5	79.8	78.4
7	77.6	78.9	82.4	80.8	93.68	84.5	82.8	80.4

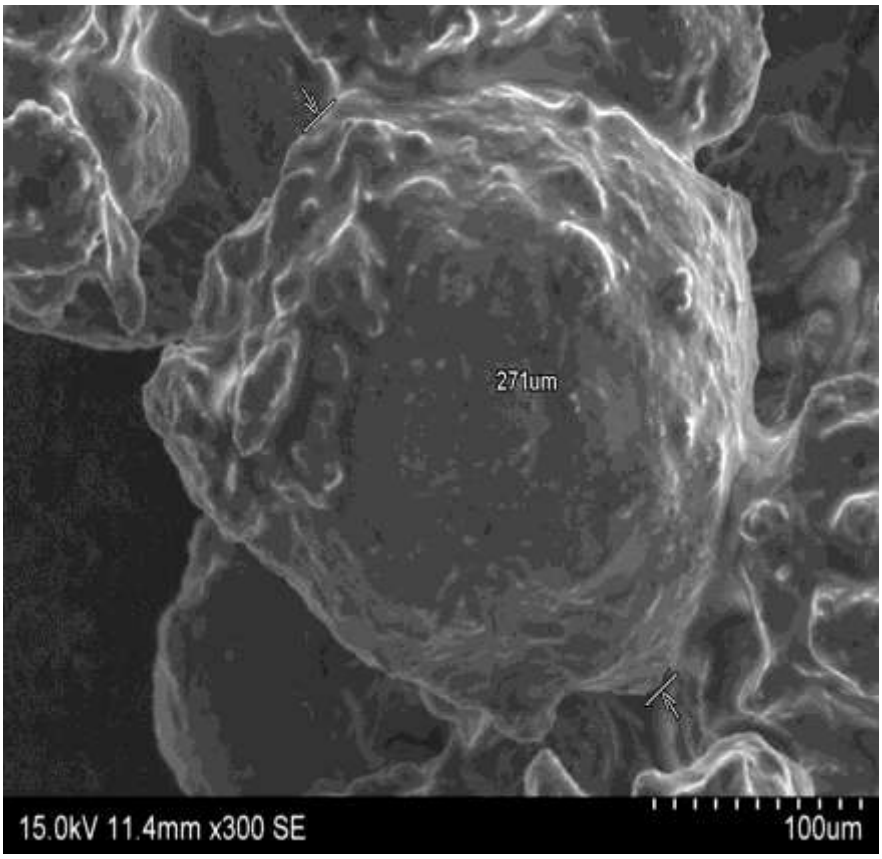

Fig: 01 Pictogram of spherical shape particles (SEM)

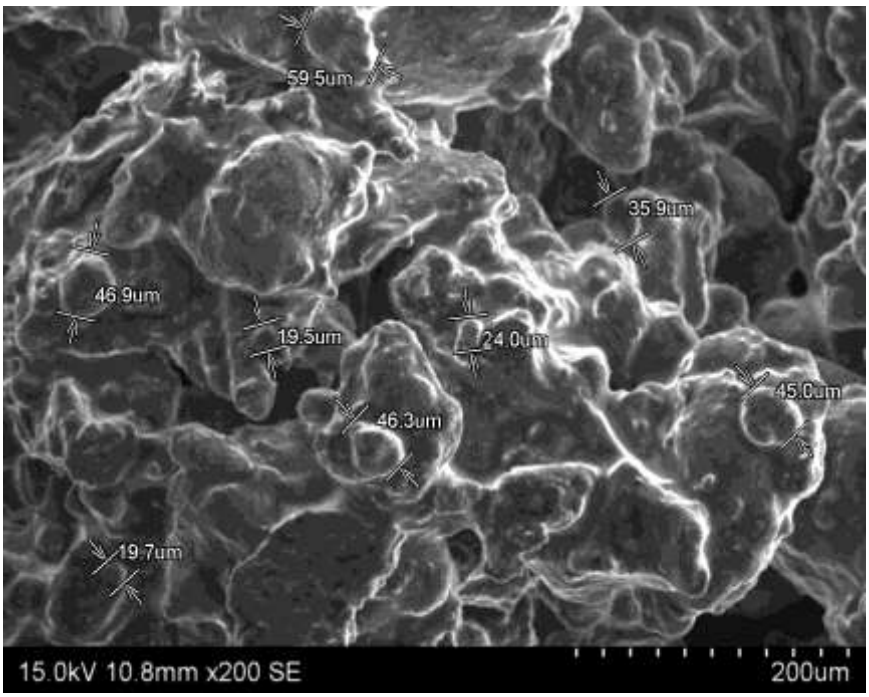

Fig: 02 Pictogram of surface morphology of Ranolazine microcapsules in micron range (SEM)

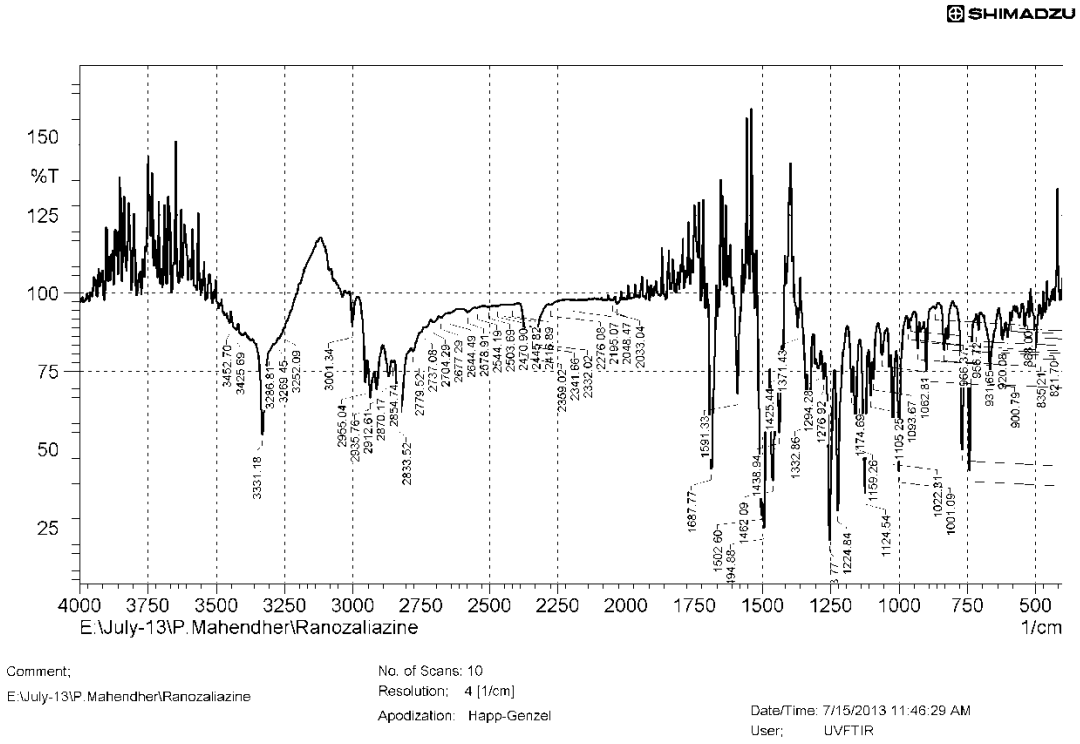

Fig 03: FTIR spectra of drug-Ranolazine

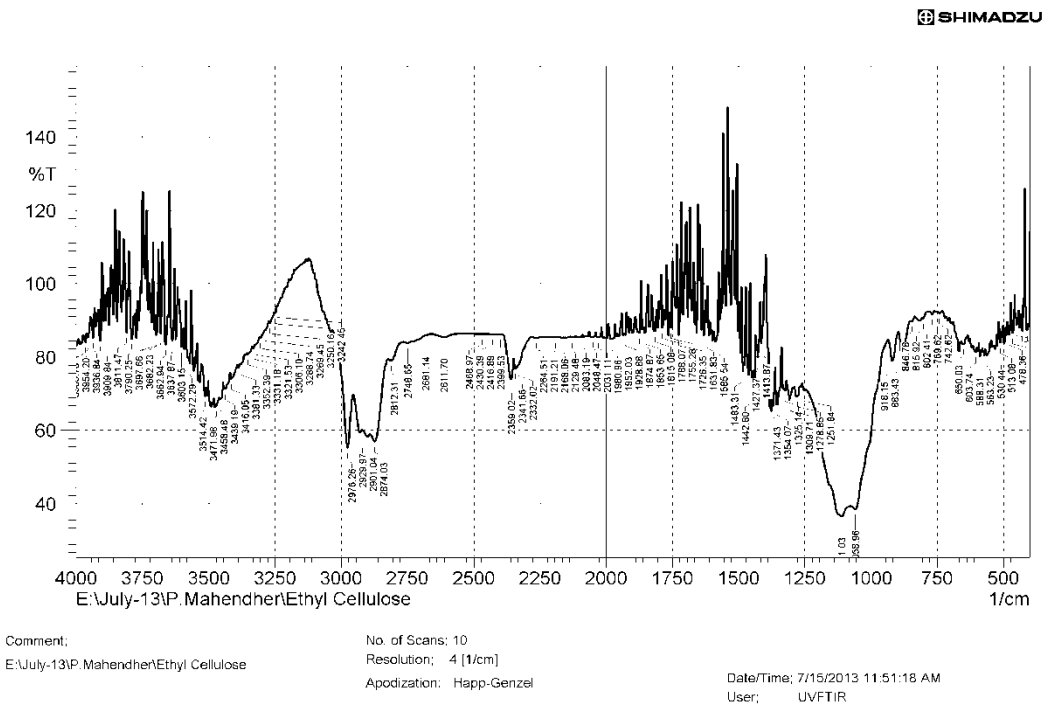

Fig 04: FTIR spectra of Physical mixture

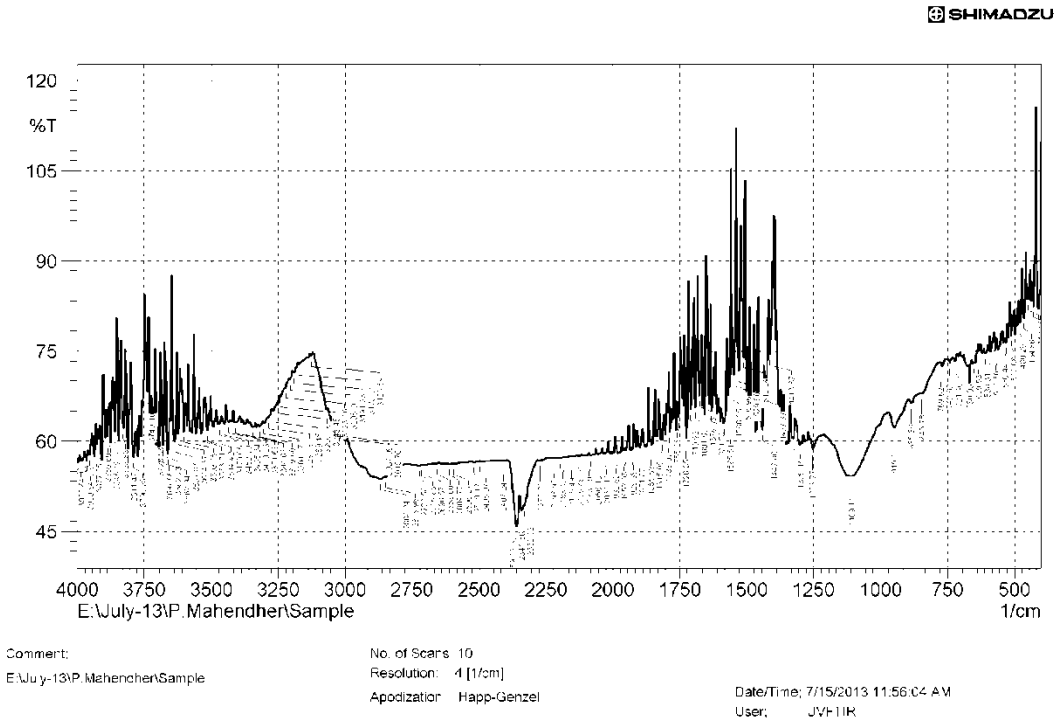

Fig 05: FTIR spectra of Optimized microcapsule F5

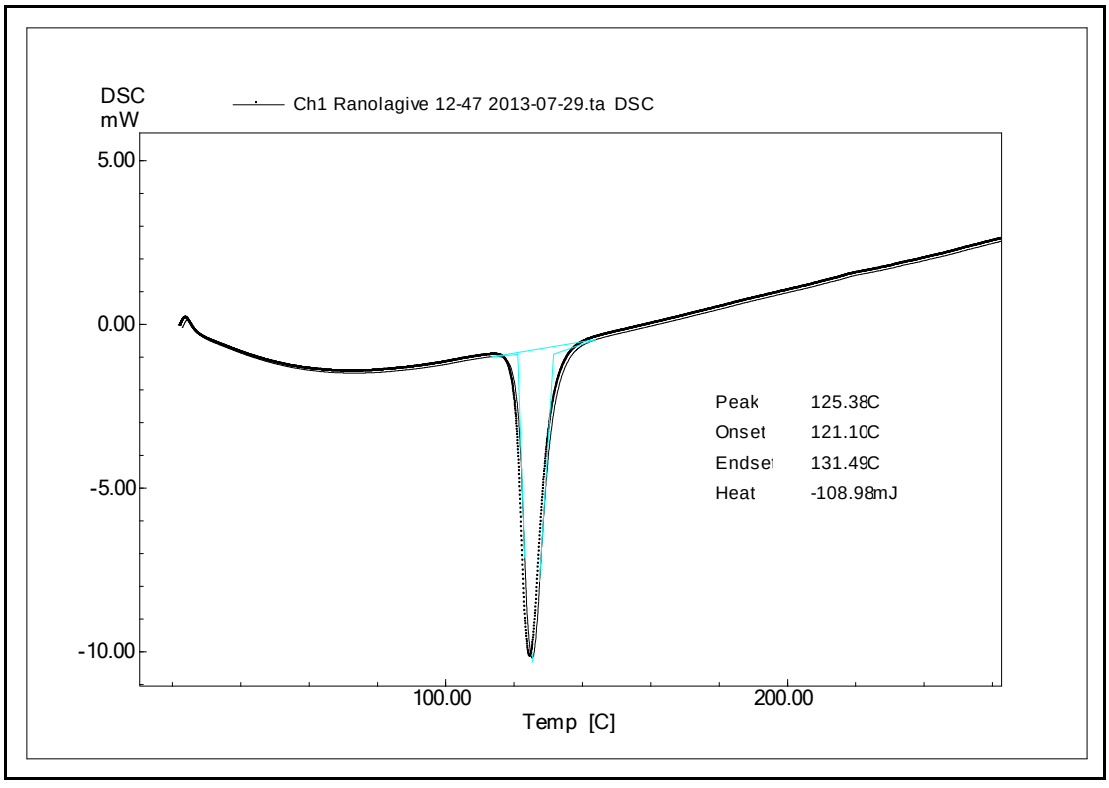

Fig: 06 Thermogram of drug-Ranolazine

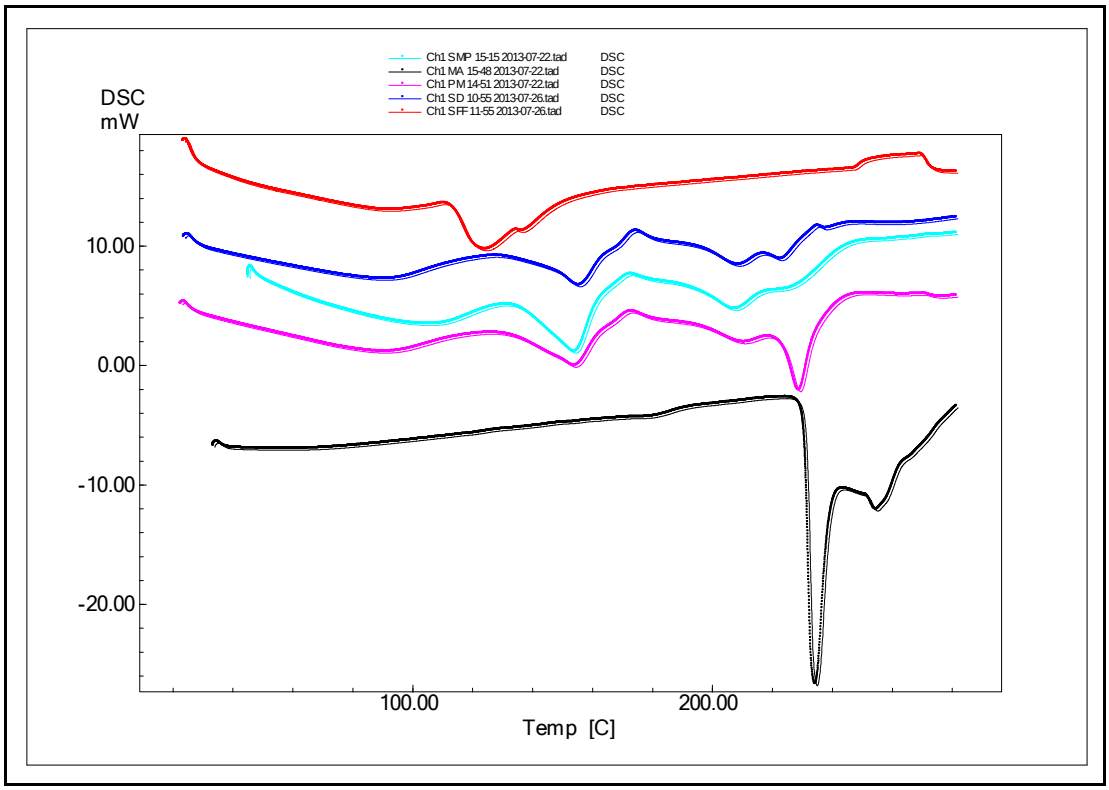

Fig: 07 Thermogram of different drug formulations and optimized formulation F5

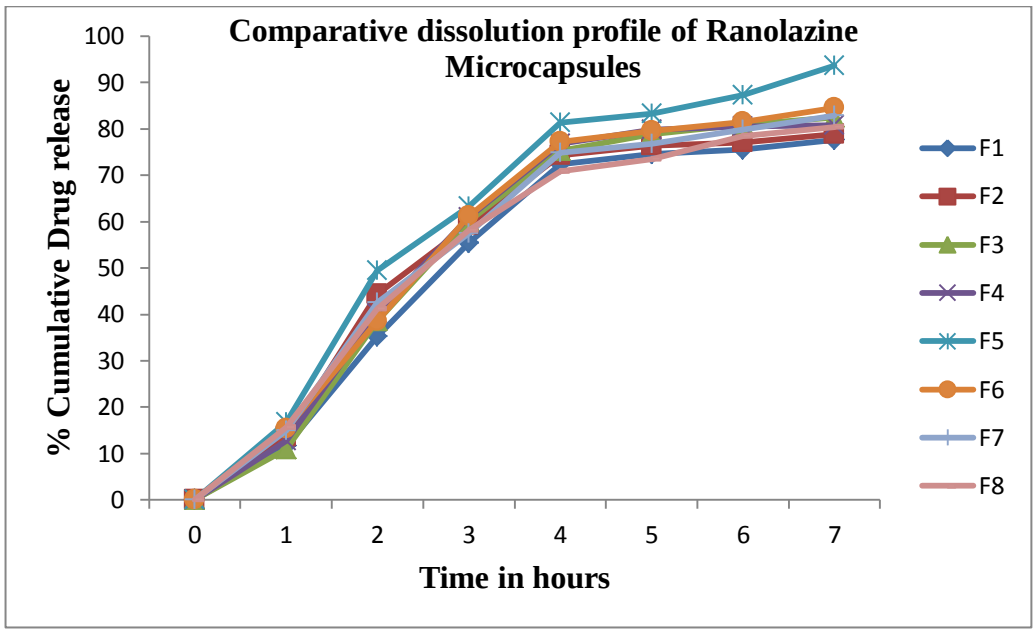

Fig: 08 Comparative dissolution profile of Ranolazine microcapsules

Conclusion

All the particles are in micron range and with high entrapment efficiency and percentage yield with sustain release of drug is for 7 hours. Thus, we can conclude that prepared Ranolazine ethyl cellulose-HPMC microcapsules prepared by w/osingle emulsification-solvent evaporationhave the property to release the drug in sustained manner.

Acknowledgements

The authors would like to acknowledge management of Mother teresa college of pharmacy for providing necessary support to the conduction of this work. Also, the authors would like to acknowledge Department of technology, Osmania university, Hyderabad, for providing analytical support to this project.

References

1. Yie W. Chein,*Novel Drug Delivery Systems*, Second Edition, Revised and Expanded, Marcel Dekker, INC. New York, Basel, Hong Kong, 139-196.
2. Joseph R. Robinson, Vincent H. L. Lee, *Controlled Drug Delivery fundamental & applications*, Second Edition, Revised and Expanded, Marcel Dekker, INC. New York, 581-590.
3. *Targeted and Controlled Drug Delivery: Novel Carrier Systems*, S.P. Vyas, R.K, Khar,CBS Publishers, New Delhi, 2002, 425-441.
4. Deasy, PB, 1984, *Microencapsulation and related drug process* (New York: Marcel Dekker Inc. 1996).
5. Birnbaum DT, BrannonPeppas L, *Microparticle drug delivery systems, Drug delivery systems in cancer therapyIn: Brown DM, editor*, Totowa: Humana Press Inc; 2003. pp. 117-136.
6. Wei Wang, Xiudong Liu, Yubing Xie, Hua'an Zhang, Weiting Yu, Ying Xiong, Weiyang Xie and Xiaojun Ma,Microencapsulation using natural polysaccharides for drug delivery and cell implantation, *Journal of Materials Chemistry*, June 2006;16,3252-3267.
7. Jaspreet kaur vasir, kaustubh tambwekar, sanjay gang Bioadhesive microspheres as controlled drug delivery system, *International journal of pharmaceutics*, 2003; 255 13-32.
8. Donbrow M, Recent advances in microcapsule delivery systems. In: Breimer DD, editor. *Topics in pharmaceutical sciences, Amsterdam : Elsevier Science*; 1987, pp. 33-45.
9. Hassan Sawalha, Karin Schroen, Remko Boom, Biodegradable polymeric microcapsules: Preparation and properties,*Chemical Engineering Journal*, 169, 2010, 1-10.
10. Santhosh Kumar, Chowdary K.A and Sammaiah G; Controlled Release Formulation and Evaluation of Aceclofenac by Microencapsulation; *Pharmanest - An International Journal of Advances in Pharmaceutical Sciences:* Vol.2, (2-3) March-June2011.
11. Bansode SS, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. Microencapsulation: a review.*International Journal of Pharmceutical Sciences Review and Research.*2010; 1: 38–43.
12. I. Ilic, R. Dreu,, M. Burjak, M. Homar, J. Kerc, S. Srcic, Microparticle size control and glimepiridemicroencapsulation using spray congealing technology,*International Journal of Pharmaceutics*,May- 2009; 381, 176–18.
13. Ravikumar M.N.V. 2000, Nano and microparticles as controlled drug delivery devices, *Journal of Pharmacy and Pharmaceutical Sciences*, 3: 234-58.
14. Sing-Muk Ng, Jeong-Yeon Choi, Hyung-Soo Han, Jeung-Soo Huh, Jeong Ok Lim.Novel microencapsulation of potential drugs with low molecular weight and high hydrophilicity: Hydrogen peroxide as a candidate compound, *International Journal of Pharmaceutics*,2009;384(2010):120–127.
15. James Swarbrick, James C. Boylan.*Encyclopedia of Pharmaceutical technology*, Volume 12, New York (NY), Marcel Dekker, Inc; 1995.
16. Perumal D. Microencapsulation of Ibuprofen and Eudragit RS 100 by solvent diffusion technology,*International journal of pharmaceutics*, 2001; 218; 1-11.
17. Ming Li, Olivier Rouaud, Denis Poncelet, Microencapsulation by solvent evaporation: state of the art of engineering approaches, *International journal of pharmaceutics,* 363 (2008) 26-39.
18. Fuku shima S, Kishimoto S, Takeuchi Y, Fukushima M. Preparation and evaluation of o/w type emulsions containing antitumor prostaglandin. *Adv Drug Delivey Rev. 2000; 45:65–7 5.*
19. Amelie Gaignaux, Jonathan Ref, Florence Siepmann, Juergen Siepmann, Carine De vriese, Jonathan Goole, Karim Amighi, Development and evaluation of sustained-release clonidine-loaded PLGA microparticles, *International journal of pharmaceutics,* 437 (2012) 20-28.
20. Patrick B O Donnell, James W Mc Ginity, Preparation of microspheres by solvent evaporation technique ,*Advanced drug delivery review*, 1998; 28 ; 25-42.
21. Simi Sp, Saraswathi R, Sankar C, Krishnan Pn, Dilip C, Ameena K, Formulation and evaluation of Albendazole microcapsules for colon delivery using chitosan, *Asian pacific Journal of Topical Medicine*(2010) 374-378.

22. S. K. Prajapati,Purnima Tripathi, Udhumansha Ubaidulla, and Vikas Anand; Design anddevelopment of gliclazide mucoadhesive microcapsules: *In-vitro*and *In-vivo* Evaluation; *AAPS PharmSciTech*, Vol. 9, No. 1, March 2008:224-230.
23. K.P.R. Chowdaryand Y. Srinivasa Rao, Design and*in-vitro* and *in-vivo*evaluation ofmucoadhesive microcapsules of glipizide for oral controlled releasel, *AAPS PharmSciTech* 2003; 4 (3).
24. Yadav A.V., Shete A.S., Dabke A.P., Shinde V.R. Formulation and *in-vitro* evaluation of aceclofenac microcapsules. *Int. J. Pharm. Tech. Res*, 2009, 1: 135-138.

*****