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Formulation and Evaluation of Sustained Release Omeprazole Microcapsules

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Keywords: Omeprazole, sustained release, microcapsule, hydroxyl propyl methyl cellulose, ethyl cellulose and zero-higuchi-order.

ABSTRACT

Objective: The aim and of the project was to prepare and evaluate omeprazole microcapsules for sustained release properties. **Methods:** In the present study Omeprazole sustained release microcapsules were successfully prepared using different ratios polymers ethyl cellulose (EC) and hydroxy propyl methyl cellulose (HPMC-K4M) and tween-80 as emulsifying agent by w/o emulsification-solvent evaporation technique. **Results and discussion:** The prepared microcapsules were evaluated for particle size, shape, drug content and in-vitro drug release. It was observed that particle size decreased, increased entrapment efficiency and increase in dissolution rate, but also achieves sustained release of drug with increase in concentration of hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose. The percentage yield was determined. Based on the drug release data an optimized formulation, having maximum drug release was selected. The optimized formulation was characterized for particle size and surface morphology using optical microscopy method and scanning electron microscopy method (SEM). The surface of the optimized formulation was smooth and particles are spherical in micron size. Drug polymer compatibility using DSC and Fourier transform infra-red studies (FTIR). Fourier transform infra-red studies indicated that polymers selected in the study are chemically compatible with the drug. Differential scanning calorimeter studies indicated that the drug changed its physical formulation in the presence of combination of polymers. The percentage drug release of optimized formulation was compared with the percentage drug release of pure drug. Omeprazole release rate was observed highest with the highest concentration of HPMC-K4M, used in the present studies. When percent of HPMC-K4M was increased, the particle size of microcapsules was decreased. Microcapsules showed sustained release in pH 6.8 phosphate buffer for up to 12 hrs. From the formulation F1 to F8, F5 showed high dissolution profile. The data obtained from the dissolution profiles were compared in the different release kinetics models and the regression coefficients were compared. The drug release profile follows Zero and higuchi order release. It was found that optimized formulation of omeprazole microcapsules showed sustained release data. All the results are reported. **Conclusion**: Thus we can conclude that prepared ethyl cellulose and HPMC microcapsules have the property to release the drug in sustained manner. Hence, these microcapsules are sustain release microcapsules prepared by single emulsification technique (W/O)-solvent evaporation by microencapsulation method.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic 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)[1]. The concept of designing specified delivery system to achieve selective drug targeting has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a "magic bullet". Sustained & novel delivery envisages optimized drug in the sense that the therapeutic efficacy of a drug is optimized, which also implies nil or minimum side effects. It is expected that the 21st century would witness great changes in the area of drug delivery. The products may be more potent as well as safer. Target specific dosage delivery is likely to overcome much of the criticism of conventional dosage forms. The cumulative outcome could be summarized as optimized drug delivery that encompasses greater potency & greater effectiveness, lesser side effects and toxicity, better stability, low cost hence greater accessibility, ease of administration and best patient compliance (Jain N K., 2001)[2]. The efficacy of a drug in a specific application requires the maintenance of appropriate drug blood level concentration during a prolonged period of time. So the concept of sustained drug release has emerged from the need for effective management of diseases. 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 up-hold constant drug concentration in blood for a prolonged period of time. Microencapsulation has played a vital role in the development of sustained release drug delivery systems. "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 onset of its pharmacologic action is the often delayed and the duration of its therapeutic effects is sustained. A sustained release is facilitated through the consistent rejuvenation of drug molecules. By the sustained release method, therapeutically effective concentration can be achieved in the systematic circulation over an extended period of time, thus achieving better compliance of patients sustained release products often eliminate the need for night dosing as it provided sustained plasma drug levels which benefits not only the patients but the care given as well. 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[3]. The various approached or the novel drug delivery systems of sustained drug delivery system includes liposomes, microspheres, nanoparticles etc. Particulate delivery systems (microspheres, nanoparticles) score over liposomes and are looked as alternative to liposomes. The production of drug loaded polymeric implant, wafer, microspheres and hydrogel introduced a new concept in drug administration. 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, microsphres, liposomes etc[6]. Microcapsules have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and sustained drug release[4]. 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.

A ‘microcapsule’ may be defined as a spherical particle with size varying from 1 to 1000µm containing a core substance. 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, for example, ‘microbeads’ and ‘beads’ alternatively as shown in figure-1. 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[7]. Microencapsulation is one of the newly developed technique[5]. Microencapsulation is a process of incorporating drugs into small size multi particulate units. As a process it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids. Microencapsulation developed for use in medicine consists of solid or liquid core material containing one or more drugs enclosed in coating material. 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 of Bugerberg dejong and coworkers 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. This process of microencapsulation has been used medically for the encapsulation of live cells and vaccines[6,7].

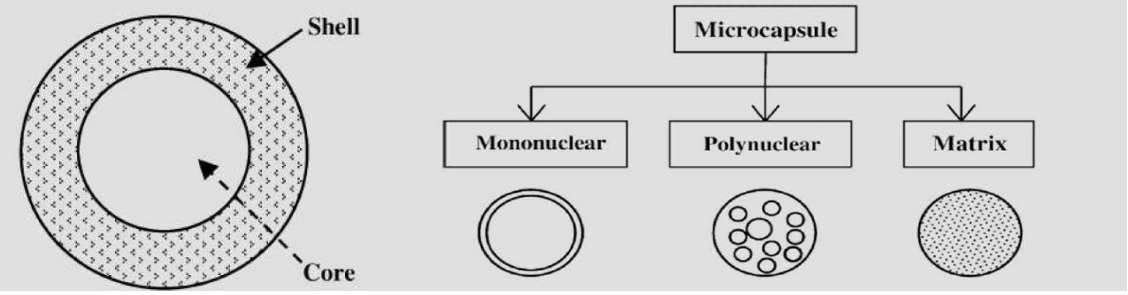

Figure 1: Morphology of microcapsules with core and shell.

Different methods of preparation of microcapsules are employed for the preparation of microcapsules. They include, solvent evaporation, single emulsion method, double emulsion method, polymerization technique, conventional polymerization, interfacial polymerization, phase separation co-acervation technique, spray drying and spray congealing, solvent removal, solvent extraction, freeze drying, chemical and thermal cross linking, precipitation, hot melt microencapsulation method, multiorifice centrifugal process, pan coating, air suspension coating and melt-dispersion technique as shown in table-1[8,9].

Table 1: Microencapsulation technologies with their relative particle size

Physicochemical processes	**Relative particle size range**	**Physicomechanical processes**	**Relative particle size range**
Coacervation	2-1200 µm	**Spray drying**	5-5000 µm
Polymer-polymer incompatability	0.5-1000 µm	**Fluid bed technology**	20-1500 µm
Solvent evaporation	0.5-1000 µm	**Pan coating**	600-5000 µm
Encapsulation by super critical fluid		**Spinning disc**	5-1500 µm
Phase inversion	0.5-5.0 µm	**Co extrusion**	250-2500 µm
Hot melt	1-1000 µm	**Interfacial polymerization**	0.5-1000 µm
Encapsulation by poly electrolyte multilayer	0.02-20 µm	**In-situ polymerization**	0.5-1100 µm

Different types of microcapsules area albumin microcapsules, gelatin microcapsules, starch microcapsules, dextran microcapsules, PLGA microcapsules, polyphosphazene microcapsules, polyanhydride microcapsules, chitosan microcapsules, carrageenan microcapsules, alginate microcapsules, poly (alkyl cyanoacrylate) microsphere and poly acrolein microcapsules. Most attempts to increase encapsulation efficiency are based on a common idea that fast polymer precipitation on the surface of the dispersed phase can prevent drug loss into the continuous phase (Bodmeier and McGinity, 1988). On the other hand, when solidification of the dispersed phase is delayed, encapsulation efficiency becomes low because more drugs diffuse into the continuous phase. Factors influencing encapsulation efficiency are molecular weight of polymer, polymer concentration and hydrophilicity of polymer. The active components are loaded over the microcapsules principally using two ways, during the preparation of microcapsules and after the formulation of microcapsules by incubating them with the drug or protein. Drug can be loaded by means of physical entrapment, chemical linkage and surface adsorption[10,11].

Different applications of microencapsulation are taste and odor masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against the environment (moisture, light, heat, and/or oxidation) and vice versa (prevention of pain on injection), Delay of volatilization, separation of incompatible materials (other drugs or excipients such as buffers), improvement of flow of powders, safe handling of toxic substances, aid in dispersion of water-insoluble substances in aqueous media, production of sustained-release and targeted medications and reduced dose dumping potential compared to large implantable as shown in table-2[12,13].

Table 2: List of some drugs which were investigated as marketed microcapsules:

S.No	Drug	Polymer	Result	Method	Use
I. Anticancer and Antitumor					
01	Oxantrazol	Chitosan	Enhance the delivery of drug in brain 100 times	Combined emulsion	Anticancer
02	Mitoxantrone	Glutaraldehyde-Saturated toluene	Minimize drug toxicity & maximize therapeutic efficacy	Cross linking technique	Antitumor
03	Fluorouracil	Glutaraldehyde, Chitosan, Chitin	Slow-down of release rate of drug Reduce release rate	O/W/O emulsion system	For targeted delivery to treat cerebral tumors Antitumor activity
04	Cisplatin	Glutaraldehyde, Chitosan, Chitin	Slow-down of release rate of drug Reduce release rate	O/W/O emulsion system	For targeted delivery to treat cerebral tumors Antitumor activity
II. NASID					
05	Ketoprofen	Chitosan	Modulate drug release	Multiple emulsion (o/w/o)	Anti-inflammatory
06	Diclofenac sodium	Chitosan, Chondroitin sulphate	Suppress the release rate	Co-acervation phase sepration	Anti-inflammatory
07	Aceclofenac	Eudragit	Controlled release and minimize local side effect	By dissolving drug in polymer	Anti-inflammatory drug
08	Indomethacin	Chitosan	Decrease in the release rate	Co-matrix method	Anti-inflammatory drug
III. Antibiotic					
09	Amoxicillin		Slow release rate	Crosslinking	For helicobacter pylori infection eliminating infection
10	Gentamicin	PLGA and PCL	Controlled release	Double emulsion	Antibiotic

				technique	
IV. Cardiac agent					
11	Dilitazam	Casein, chitosan	Retard drug release	Colloidal co-acervation technique	Calcium channel blockers
12	Propranolol	Chitosan	Enhance Drug encapsulation efficiency	Emulsification co-acervation technique	Calcium channel blockers
13	Nifedipine	Chitosan	More drug entrapment efficiency	Encapsulation	Calcium channel blockers
V. Steroidal					
14	Progesterone	Glutaraldehyde, chitosan	Maintain plasma drug concentration	Crosslinking	Steroid
VI. Anti-diabiatic agent					
15	Insulin	Chitosan	Improve systemic absorption	Crosslinking	Anti-hyperglycemic effect
VII. Diuretics					
16	Furosemide	Chitosan	Reduce effect of external variables	Crosslinking	Diuretics

MATERIALS AND METHODS

Omeprazole is a gift sample from Nosch laboratories pvt limited, ethyl cellulose, HPMC K4M, tween-80, light liquid paraffin, dichloromethane, methanol, n-hexane are from SD fine chemicals are analytical grade (AR) grade. The preformulation studies with the lansoprazole obtained were performed using conventional and reported techniques. The UV-Visible spectrum, solubility, flow properties, drug crystallinity were determined[14,15].

Preparation of omeprazole loaded ethyl cellulose-HPMC-K4M microcapsules:

Single emulsification method (W/O) & solvent evaporation method was employed in the preparation of omeprazole loaded ethyl cellulose-HPMC-K4M microcapsules. This method for preparation of microcapsules was reported to overcome the problem of low encapsulation efficiency of water soluble drug prepared by water/oil emulsion solvent evaporation method. Polymer (ETHYL CELLULOSE-HPMC-K4M)] is dissolved in organic phase dichloromethane (DCM). In this organic phase, aqueous drug solution is emulsified using magnetic stirrer operating around 4 hours to prepare water /oil (w/o) primary emulsion. This primary emulsion is added to external aqueous phase containing surfactant tween-80 with stirring by magnetic stirrer (Remi laboratory instuments, East Mumbai, Maharashtra, India-

400063) for one hour at 1500rpm as shown in table-3. The microcapsules obtained is collected by centrifugation, filtered and then dried. The dried microcapsules are hardened by n-hexane and subjected for characterization and evaluation studies[16,17,18].

Table 3: Composition of Omeprazole Microcapsules

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Omeprazole(mg)	100	100	100	100	100	100	100	100
Ethyl cellulose(mg)	1000	1000	1000	1000	1000	1000	1000	1000
HPMC K4M(mg)	250	500	750	1000	1500	1000	750	500
Tween 80(ml)	0.25	0.25	0.50	0.50	0.75	0.75	1	1
Dichloromethane(ml)	10	10	10	10	10	10	10	10
Distilled water(ml)	2	2	2	2	2	2	2	2
Drug: polymer	1:2.5	1:5	1:7.5	1:10	1:15	1:10	1:7.5	1:5
Water:organic solvent	1:5	1:5	1:5	1:5	1:5	1:5	1:5	1:5
% Calcium chloride solution in ml	15	15	15	15	15	15	15	15

Evaluation and characterization of omeprazole microcapsules[19,20,21]:

Percentage yield: Omeprazole microcapsules are dried at room temperature, weighed and the yield of microcapsules was calculated using the formula. 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 these microspheres was determined to obtain the theoretical yield.

$$\text{Percentage Yield (\%)} = \frac{\text{Practical Yield present}}{\text{Theoretical Yield}} \times 100$$

Particle size analysis: Determination of average particle size of omeprazole microcapsules with optical microscopy (Edison, India), average size of microcapsules is reported. 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 determination of average particle size of omeprazole microcapsules was reported.

Drug entrapment efficiency: The amount of drug entrapped was estimated by dissolving the 100mg of omeprazole microcapsules in dichloromethane and water in 3:1 ratio, under vigorous shaking for 1hr, the resultant solution is centrifuged, both layers were separated, omeprazole was soluble in water. The drug content in aqueous solution was analyzed spectrophotometrically by using UV-VIS spectrophotometer SL NO.00313 (Elico instruments, India) at 302nm with further dilutions against appropriate blank. The amount of the drug entrapped in the microcapsules were calculated using the formula:

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

Scanning electron microscopy: Determination of surface morphology (roundness, smoothness and formation of aggregates) of omeprazole microcapsules with polymer was carried out by scanning electron microscopy (SEM). 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 at Sura Labs Pvt Ltd, Hyderabad, Telangana. The smallest size microcapsules were used for determining surface morphology[22].

In-vitro drug release: The in-vitro release of drug from the omeprazole microcapsules formulation was carried out by using USP tablet dissolution test apparatus-XIV (Lab India Pvt, India.). 2 ml of microcapsules suspension containing known amount of drug was placed in a dissolution apparatus of reading were taken for 12 hrs. Aliquots (5ml) of release medium were withdrawn at different time intervals and the sample was replaced with fresh PBS (pH 6.8) to maintain constant volume. The samples analyzed for drug content by UV-visible spectrophotometer at 302nm. After every one week the complete medium was withdrawn and replaced by fresh medium to avoid saturation of the medium. The obtained data were fitted into mathematical equation (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[22].

In-vitro release kinetics: To analyze the in-vitro release data various kinetic models were use to describe the release kinetics. The zero order rate equation (1) describes the systems where the drug release rate is independent of its concentration. The first order equation (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on fiction diffusion. The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. **Zero-order kinetic model** – Cumulative % drug released versus time.
2. **First-order kinetic model** – Log cumulative percent drug remaining versus time.
3. **Higuchi's model** – Cumulative percent drug released versus square root of time.
4. **Korsmeyer equation / Peppa's model** – Log cumulative percent drug released versus log time[23].

FT-IR studies-Drug Excipient Compatibility Studies: The FT-IR spectra of drug, ethyl cellulose, HPMC-K4M, physical mixture and omeprazole microcapsules were obtained. Sample about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum a pressure of about 12 Psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer (Bruker India scientific pvt ltd) at Sura Labs Pvt Ltd, Hyderabad, Telangana and the IR spectrum was recorded from 4000 cm^{-1} to 625 cm^{-1} in a scan time of 12 minutes[24].

Differential scanning calorimeter (DSC)-Solid State Stability Studies: Thermal properties of the powder samples were investigated with a DSC (Hitachi, S-3700N, Tokyo, Japan) at Sura Labs Pvt Ltd, Hyderabad, Telangana. 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. Magnesia was used as the standard reference material[25].

RESULTS:

The preformulation studies of omeprazole drug were conducted and the physical properties are white to off white in appearance, crystalline powder, very slightly soluble in water, the melting range is 156°C and acid dissociation constant (pK_a) is 4.0. The omeprazole drug λ_{max} was determined by using stock solution and identified as 302nm using methanol and phosphate buffer pH 6.8 used as a blank solution. Standard graph of omeprazole was plotted as per the procedure in experimental method and its linearity is mathematically calculated.

The standard graph of omeprazole showed good linearity with R^2 of 0.998 which indicates that it obeys "Beer-Lambert'. Omeprazole loaded ethyl cellulose-HPMC-K4M microcapsules are prepared by single-emulsification (W/O) and solvent evaporation method and prepared formulations are characterized and subjected for various evaluation studies as shown in figure-2.

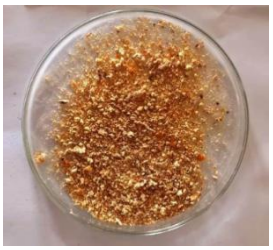

Figure 2: Products of omeprazole microcapsules.

Percentage yield was found to be highest for F8 (69.9%) formulation and least for F1 formulation. The range of all formulations F1 to F8 is between 58.3 to 69.9%. In F1 formulation the particle size was found to be 320µm and in the subsequent formulations the particle size was found to be decreased this is because of difference in concentration of polymer and emulsifying agent. Particle size was more for F1 formulation and found least for F5 (220 µm) formulation, the range is between 220 to 350 µm from F1 to F8. With increase in concentration of polymer and emulsifying agent, surface area of the microcapsules increases and thereby particle size decreases. From the results it can be concluded that there is a proper distribution of omeprazole in the microcapsules. The percentage entrapment efficiency was found to be 75 to 87%. A maximum of 87% drug entrapment was obtained in the omeprazole microcapsules of formulation F5. Surface morphology of the microcapsules was examined by SEM. The microcapsules of optimized formulation F5 were examined. Microcapsules were smooth, spherical and wavy in nature. Microcapsules were obtained in the micro range of 19.5 to 271.5 µm as shown in the figure-3.

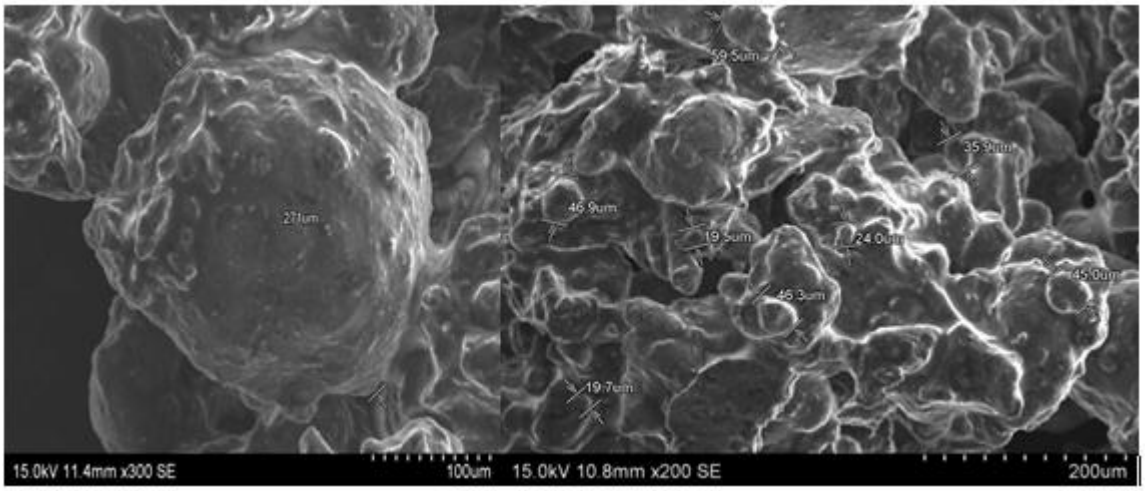

Figure 3: Surface morphology of Omeprazole microcapsules (SEM)

From the below spectra of omeprazole, formulation F5, physical mixture and polymers, it was observed that all characteristic peaks of omeprazole were present in the combination spectrum and there is no shift in peaks, thus indicating compatibility of the omeprazole and polymer as shown in figure 4 and 5. There is no physical and chemical interaction of drug and polymers. Hence there is no drug and excipient incompatibility. The drug and excipients are compatible.

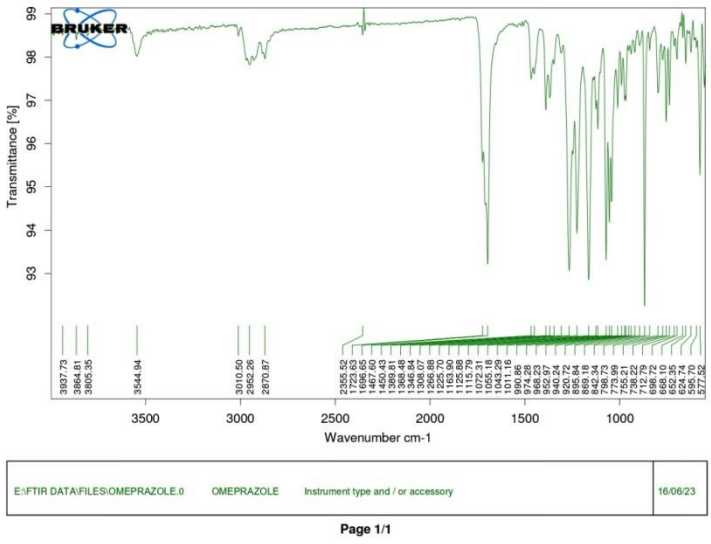

Figure 4: FT-IR studies of drug-omeprazole

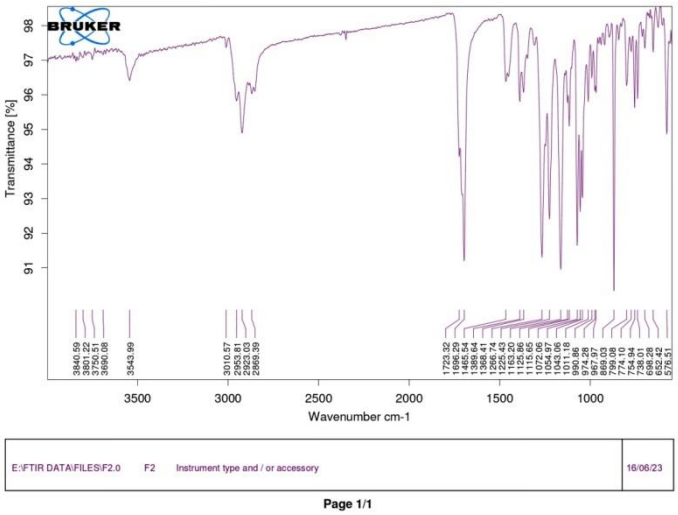

Figure 5: FT-IR of omeprazole optimized microcapsules (F5)

Differential scanning calorimeter studies were performed to understand the nature of the encapsulated drug. The physical state of omeprazole in the polymer would also influence the release characteristics. To probe this effect, DSC analysis was performed on omeprazole (drug) and omeprazole optimized formilation microcapsules F5 (product). From the DSC results it was observed that characteristic peak of drug is not observed in the formulation. Hence it indicates the physical nature of drug is changed in the formulation, the amorphous nature of drug is changed to crystalline form. DSC results are shown in the figure 6 and 7.

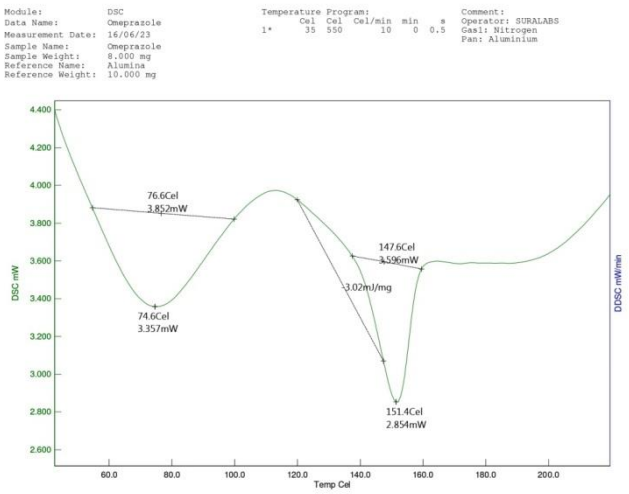

Figure 6: DSC studies of drug-omeprazole

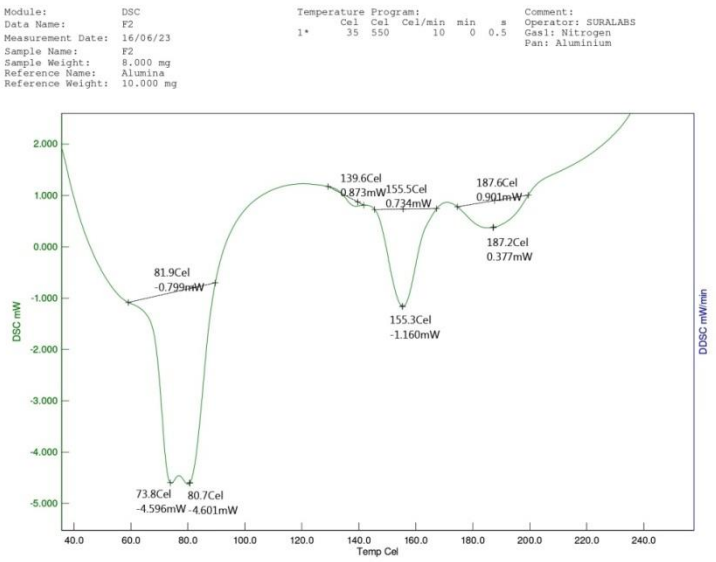

Figure 7: DSC Studies of omeprazole Optimized Microcapsules (F5)

The in-vitro dissolution profile of prepared formulations was determined by USP XIV apparatus. The dissolution was carried out for a period of 12 hrs in 6.8 pH phosphate buffer. The cumulative percent release of F1 to F8 formulations at various time intervals was calculated and tabulated. The cumulative percent drug release in all formulations was plotted against time. The maximum percent of drug release was found in F5 formulation which contains maximum drug entrapment as shown in the table 4, 5 and figure-8.

Table 4: In-vitro cumulative % drug release data of omeprazole microcapsules

Time in hours	**%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
4	55.4	59.2	60.1	60.9	63.2	61.2	57.5	58.2
6	72.4	74.3	75.3	76.8	81.27	77.2	74.8	70.8
8	74.6	76.3	78.9	79.8	83.27	79.5	76.8	73.4
10	75.6	77.1	80.93	80.5	85.27	81.5	79.8	78.4
12	77.6	78.9	82.4	80.8	92.8	84.5	82.8	80.4

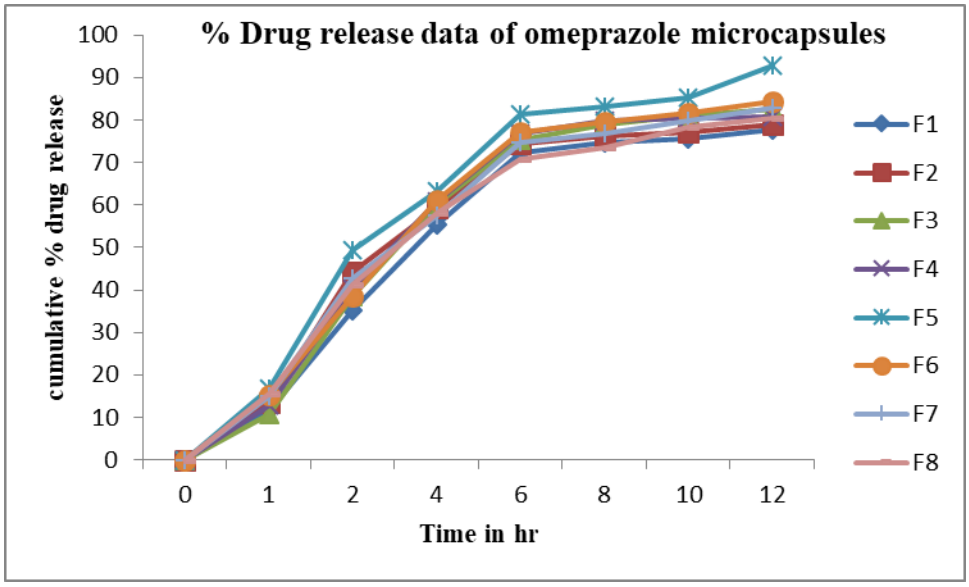

Figure 8: Comparison of cumulative % drug release of all formulations

Table 5: In-vitro cumulative % drug release of pure drug (omeprazole) and optimized microcapsule (F5):

Time	Pure drug (Omeprazole)	Optimized formulation (F5)
0 min	0	0
5 min	8.14	3
10 min	13.065	10
15 min	25.98	12
30min	34.78	15
45min	41.36	23
1 hr	49.62	16.7
2 hr		49.5
4 hr		63.2
6 hr		81.27
8 hr		83.27
10 hr		85.27
12 hr		92.8

The formulations followed the zero and higuchi order model for the drug release study. Since the formulations follow higuchi's model, thus they indicate diffusion mechanism as shown in table 6 and figures 9, 10, 11, 12 and 13. The peppa's plot showed the n-value of 0.9395 for formulation F5, thus indicating non- fickian diffusion. Thus prepared omeprazole microencapsules shows sustained release system.

Table 6: Release kinetics data profile

Order of release	Zero order	First order	Peppas	Higuchi	Hixson crowell
Correlation	0.9274	0.9723	0.9395	0.9685	0.9615
(R^2)	0.8600	0.9454	0.8827	0.9380	0.9246

Zero order release kinetics of F5:

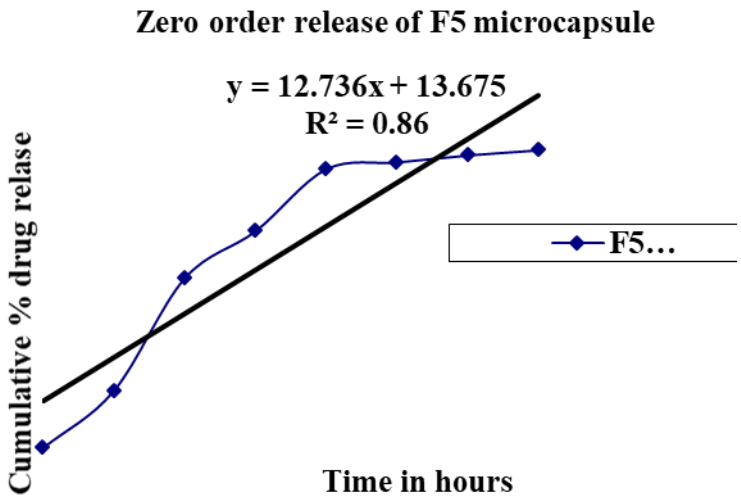

Figure 9: Zero order release of F5

First order release kinetics of F5:

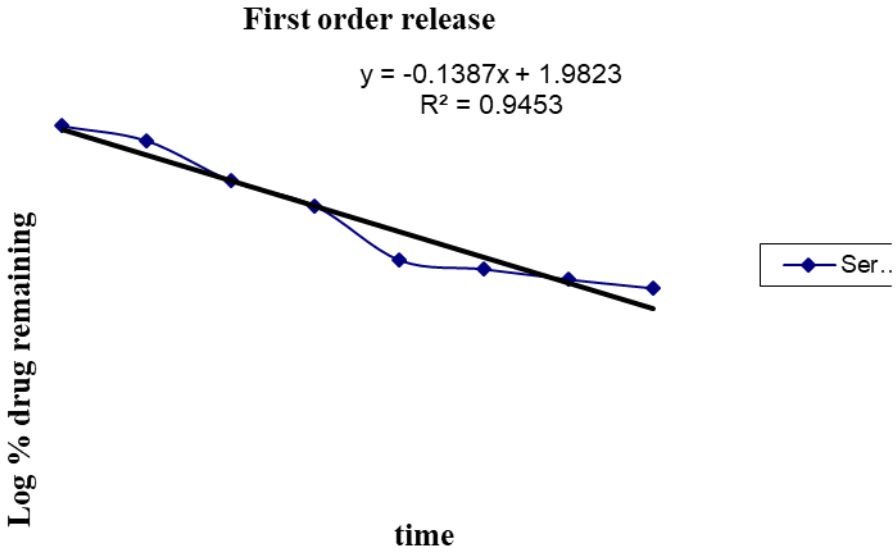

Figure 10: First order release kinetics of F5

Huguchi order release kinetics of F5:

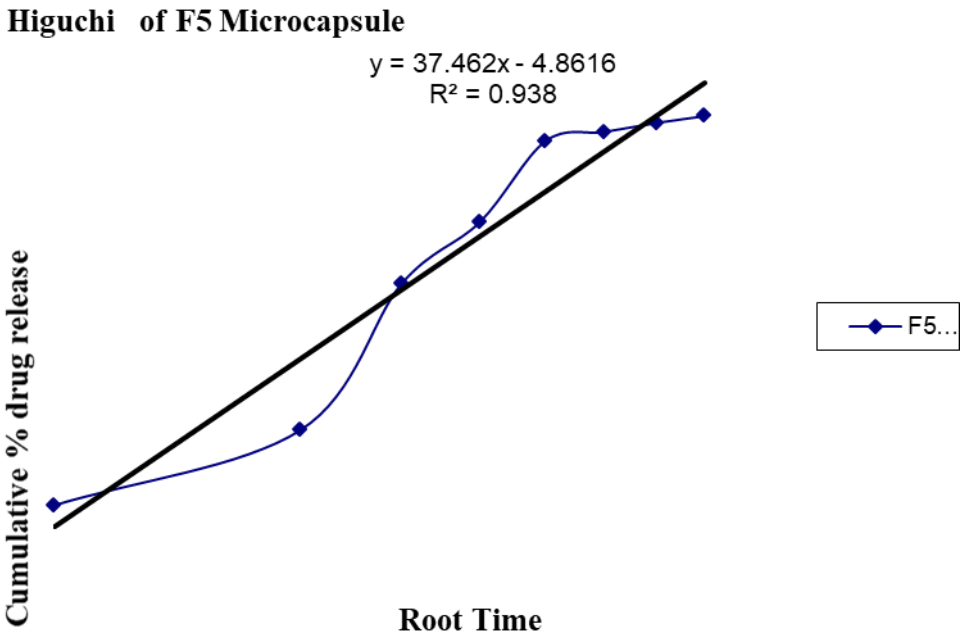

Figure 11: Huguchi order release kinetics of F5

Peppas order release kinetics of F5:

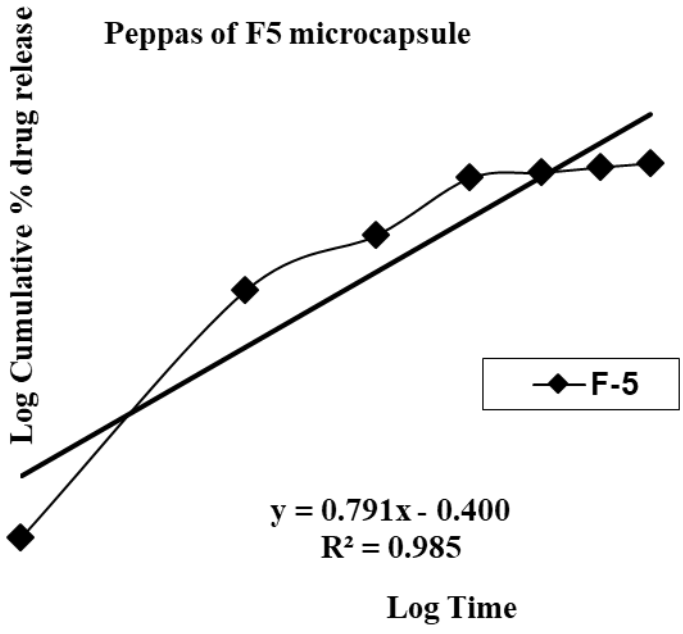

Figure 12: Peppas order release kinetics of F5

Hixson Crowell release kinetics of F5:

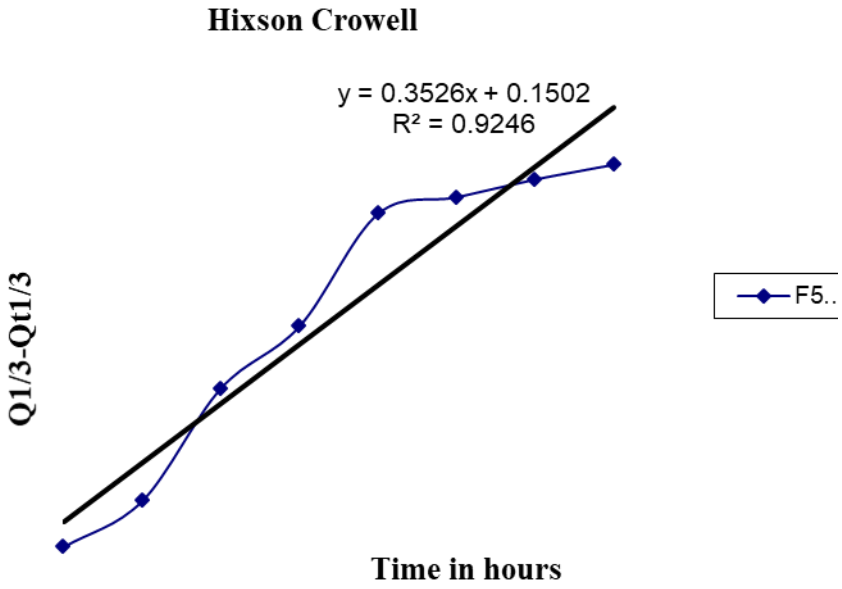

Figure 13: Hixson Crowell release kinetics of F5

DISCUSSION:

In this work an attempt was made to formulate and evaluate microcapsules for sustained release of omeprazole by single emulsification-solvent evaporation method. Low molecular weight, good permeability and shorter half-life of omeprazole made it a suitable drug candidate for the development of microencapsulation. The main objective of formulating the system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. The compatibility parameters characterization was done by FTIR & DSC methods. 8 formulations were prepared using different polymers in different ratios and combinations, along emulsifying agent and cross linking agent. The microcapsules were characterized & evaluated for prefomulation studies, particle size, SEM for surface morphology, FTIR & DSC for drug-excipient interactions and change in physical form, in vitro release were performed by using tablet dissolution test apparatus. Particle size was more for F1 formulation and found least for F5 formulation, the range is 220 µm to 350 µm by optical microscopy method. With increase in concentration of polymer & emulsifying agent, surface area of the microcapsules increases and thereby particle size decreases. Percentage yield was found to be highest for F5 formulation and least for F1 formulation. The range of all formulations F1 to F8 is between 58.3 to 69.9 %. From the results it can be inferred that there is a proper distribution of omeprazole in the microcapsules. The percentage entrapment

efficiency was found to be 75 to 87%. A maximum of 87% drug entrapment was obtained in the ranolazine microcapsules of formulation F5. Optimized F5 omeprazole microcapsules surface morphology were smooth and spherical and wavy in nature. Particles were obtained in the micro range of 19.5 to 271.5 µm by SEM. From the above spectra of omeprazole, formulation F5, physical mixture and polymers, it was observed that all characteristic peaks of omeprazole were present in the combination spectrum and there is no shift in peaks, thus indicating compatibility of the omeprazole and polymer. There is no physical and chemical interaction of drug and polymers. Hence there is no drug and excipient incompatibility, there are compatible. DSC studies were performed to understand the nature of the encapsulated drug. The physical state of omeprazole in the polymer would also influence the release characteristics. To probe this effect, DSC analysis was performed on omeprazole (drug) and omeprazole microcapsules F5 (product). From the DSC results it was observed that characteristic peak of drug is not observed in the formulation. Hence it indicates the physical nature of drug is changed in the formulation, the crystalline state of drug is changed to amorphous form. The *in-vitro* dissolution profile of prepared formulations was determined by USP dissolution test apparatus. The dissolution was carried out for a period of 12 hrs in 6.8 pH phosphate buffer. The cumulative percent release of F1 to F8 formulations at various time intervals was calculated. The cumulative percent drug release in all formulations was plotted against time in Graph. The maximum percent of drug release was found in F5 formulation which contains maximum drug entrapment. The % cumulative release was found to be 92.8%. The formulations followed the Zero order model for the drug release study. Since the formulations follow 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 omeprazole microencapsules shows sustained release property.

CONCLUSION:

The presence of ethyl cellulose and HPMC in the microcapsule reduces the initial premature drug release and ensures complete release of drug due to increased susceptibility of HPMC as hydrophilic polymer to release the drug and increase dissolution rate and EC to sustain the release of drug. All the particles are in micron range and with high entrapment efficiency and percentage yield. The sustain release of drug is for 12 hours.

Thus we can conclude that prepared ethyl cellulose and HPMC microcapsules have the property to release the drug in sustained manner. Hence, these microcapsules are sustain

release microcapsules prepared by single emulsification technique (W/O)-solvent evaporation by microencapsulation method.

ABBREVATIONS:

DCM-dichloromethane, DSC-differential scanning calorimeter, EC-ethyl cellulose, F-formulation, FTIR-fourier transform infra-red spectroscopy, HPMC-K4M-hydroxy propyl methyl cellulose, W/O-water in oil, PLGA-polylactic-co-glycolic acid, pK_a-acid dissociation constant, RPM-revolutions per minute, SEM-scanning electron microscopy, UV-ultra violet and λ_{max}- maximum wave length.

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