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RESEARCH ARTICLE
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FORMULATION OF ETHYL CELLULOSE MICROSPHERES OF IBUPROFEN AND IT'S CHARACTERIZATION

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Abstract:
Microspheres are the drug delivery system (NDDS) which is a controlled release dosage form to maintain the constantdrug concentration in plasma, as in microspheres the drug is released at a predetermined rate for extended period of time. The aim of the project was to form microspheres of ibuprofen by using ethylcellulose in various drug to polymer ratios. Ethylcellulose was usedas a carrier in formulation of Ibuprofen (a non-steroidal anti-inflammatory drug) microsphere. Various formulation techniques were performed on the prepared dosage form.Highest loading was obtained by increasing the amount of Ibuprofen with respect to polymer.

Keywords: Ethyl Cellulose, Drug Formulation, Controlled Release, Characterization, Microspheres, buprofen

Introduction:

Formulation is a process in which a drug along with other chemical substances is designed into a medical product [1]. It can also be referred as a dosage form or the drug delivery system. There are many pharmaceutical formulations and while designing any formulation,the issue of compatibility of formulative ingredients with the candidate drug, if any must be addressed. In modern era, novel drug delivery systems is being developed to overcome issues of the conventional drug delivery system such as frequent administration of drug with short half-life or poor solubility of drug. To improve the patient compliance, various types of controlled release dosage forms are present to maintain and prolong the plasma concentration of drug whilereducing the side effects by lowering the peak plasma concentration. Microspheres is one such delivery systems.

Microspheres:
Microspheres are the "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" or a structure made up of continuous phase of oneor more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level[2]. The microspheres haveparticle size of 1-1000nm [2].

Advantages of Microsphere:
Following are few of the advantages of microsphere which makes this novel drug delivery system promising.
•Microspheres are used to mask the odor or bitter taste of drug
• Microspheres can improve the stability of the drug.
• When a drug is presented in microspheres, thedosing frequency can bereducedtherefore, improves patient compliance
• A drug in microspheres demonstrated better absorption in GIT
• The gastric irritation could be addressed when such drugs can be presented as microspheres.
• Microspheres reduce the first pass metabolism
• A drug in microspheres are with enhanced biological half-life
• Microspheres improve bioavailability
• Increased therapeutic efficacy and prolonged duration of action have been reported for thedrugs in microspheres.
• Microspheres can facilitate, controlled, sustained and targeted drug delivery
• Microspheres can simply be injected into body because of small size and spherical shape.[3, 4]

Types of Microspheres:
Microspheres are generally classified into following types (Fig. 1).

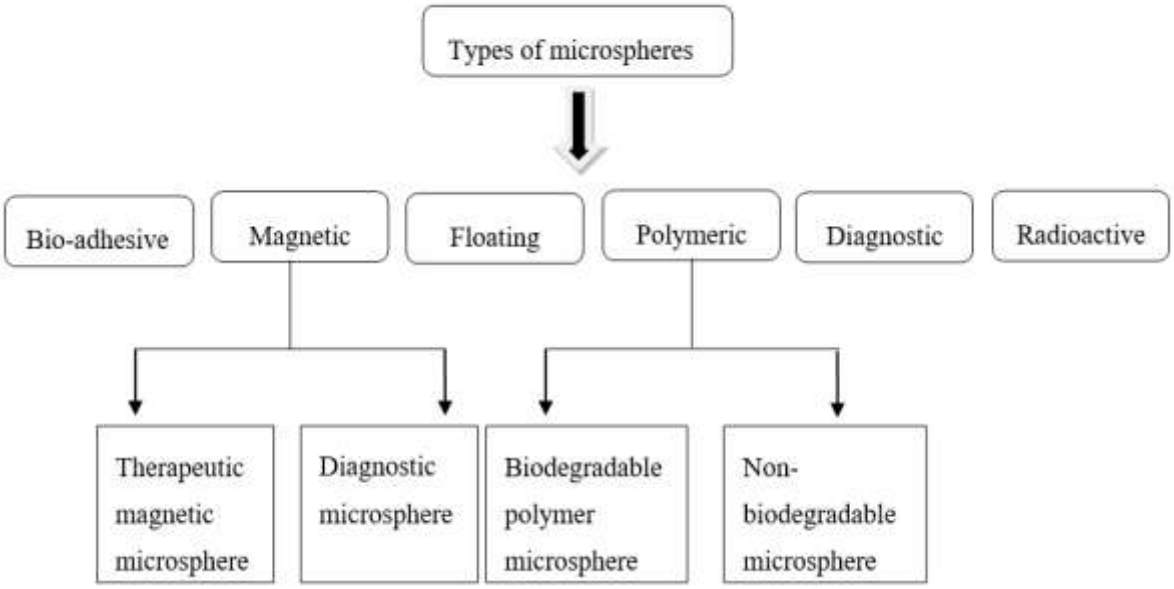

Figure 1: Types of microsphere

Bio adhesive Microspheres:
Adhesion is the sticking of drug to a membrane by using the sticking property of the water- soluble polymers. Adhesion of drug delivery device to the mucosal membrane such asbuccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds' ofmicrospheres exhibit a prolonged residence time at the site of application and causes intimatecontact with the absorption site, thereby show better absorption and thus, produces better therapeutic action [5].

Magnetic Microspheres:

This kind of delivery system localizes the drug at the disease site under the influence of a magnate.In this waylarger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers of drug receive magnetic responses to a magnetic fieldfromthe incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.The magnetic microspheres be therapeutic magnetic and diagnostic microspheres [5].

Therapeutic Magnetic Microspheres
The therapeutic magnetic microspheres are is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this delivery system [5].

Diagnostic Microspheres
The diagnostic microspheres can be used for imaging liver metastases and can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides [5].

Floating Microspheres:
In floating type microspheres, the bulk density of the dosage form is made lesser than the gastric fluid and so it remains buoyant in stomachwithout affecting gastric emptying rate. The drug is released slowly at the desired rate from such systems. Furthermore,the system remains floated onthe gastric contents and the gastric residence time is increased for better drug absorption. Moreover,there are lesser chances of dosedumping, a problem of unpredictable release of a larger amount of drug from the delivery system. Floating microspheres cab be used to produce prolonged therapeutic effects with reduced dosing frequencies [5].

Polymeric Microspheres:
The different types of polymeric microspheres can be classified as follows and they arebiodegradable polymeric microspheres and synthetic polymeric microspheres.

Biodegradable Polymeric Microspheres
Natural polymers such as starch are used with the concept that they are biodegradable,biocompatible, and bio-adhesive in nature. Biodegradable polymers prolong theresidence time when contact with mucous membrane due to its high degree of swellingproperty with aqueousmedium, results gel formation. The rate and extent of drug release iscontrolled by concentrationof polymer and the release pattern in a sustained manner. Themain drawback is in clinical use drug loading efficiency of biodegradable microspheres iscomplex and is difficult to control the drug release [5].

Synthetic Polymeric Microspheres
The synthetic polymeric microspheres are widely used in clinical applications, moreover they are also used as bulking agent, fillers, embolic particles drug delivery vehicles,etc. and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, is there tendency to migrate away from the injection site and having potential risk of embolism and further organ damage [5].

Diagnostic Microspheres:
Diagnostic microspheres are used for imaging the liver metastases and can be used to differentiate bowel loops from abdominal structures by formation of nano size particles supramagnetic iron oxides [5].

Radioactive microspheres:
Radioactive microspheres are useful for many therapies once the encapsulated diagnostic radioisotopes have been exchanged for therapeutics from the-or β-emitter group. It is used for

treatment of rheumatoid arthritis, liver tumors and cystic brain tumors. However, their use remains experimental because of smaller than expected target uptake, unwanted toxicity and insufficient treatment effects that have resulted from radio chemical instability and suboptimal biodistribution of the radiopharmaceutical [5].

Polymers used in microspheres:

There are many polymers used for microspheres but every polymer act differently. The purpose of our research is to sustain the release of ibuprofen. Due to the availability and the mechanism of ethyl cellulose, we selected it. Ethyl cellulose compactness and porosity plays key role in drug release from such hydrophobic materials like ibuprofen [5].

Polymer	**Mechanism**
Modified starch, HPMC, Carbopol 974P	Slower release of drug
Ethyl Cellulose	Controlled release for longer period.
PLGA, Chitosan	Vaccine delivery
PLA, PLGA, Starch cyanoacrylate etc.(PEG-) liposomes	Drug delivery without toxic sideeffects.
Magnetic polystyrene microspheres	Specific cell labelling
Polymer resins such as Agarosepolyacroline, sephadex	Affinity chromatography
Chitosan coated PlGA microspheres	Targeted drug delivery
Polyvinyl alcohol, polyacrylamide	Adsorption of harmful substances in blood

Table 1: Polymers used in microsphere

Candidate Drug:

Ibuprofen **(RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid** is a non-steroidal anti-inflammatory drug, which have analgesic and mild anti-pyretic effect. It has a short half-life (1-3 hours) [6]. Ibuprofen as an anti-inflammatory, inhibits the lipoxygenase pathway by acting on cyclooxygenase, which leads to the lesser production of leukotrienes by the leukocytes and synovial cells. Gastrointestinal bleeding, peptic ulceration, hypersensitivity reactions and liver problems are the most reported adverse effects. Also, ibuprofen is a class II drug as per BCS classification giving us poor solubility in acidic medium [7]. Sustained release formulation of ibuprofen will reduce these toxicities by maintaining constant plasma drug concentration [8].

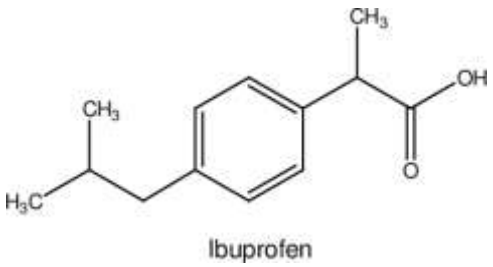

Figure 2: structure of Ibuprofen

Aims and objectives:

The aim of study was to formulate ethyl cellulose microspheres of ibuprofen, so we could achieve a sustained effect. To obtain our aim following were our objectives:

1) To formulate the microspheres of ibuprofen
2) To characterize ibuprofen by pre-formulation studies
3) To characterize the formulated microsphere by conducting post formulation tests

Literature Review:

An ideal dosage form not only achieves the therapeutic effect immediately but also maintains the drug plasma concentration for desired period of time. In case of conventional dosage form this is only possible with multiple dosing at frequent intervals depending upon the half-life of API. Dueto limitations of conventional dosage form new drug delivery systems are required which willmake the drug safer and effective through controlled and targeted delivery of drug e.g. NDDS. Such drug delivery systems optimize drug, improve patient compliance, reduce fluctuations, reduce cost and leads to development of new dosage forms.

Microspheres are being prepared globally due to their vast beneficial effects. Microspheres canbe prepared by several methods but Emulsion-Solvent Evaporation is the most acclaimed and used method for the preparation of Ibuprofen microspheres [9]. Use of polymer is common in all the methods but when sodium alginate (polymer) is added to the drug by modified emulsification method produces best quality microspheres.Due to our ease and feasibility we preferred sodium carboxymethyl cellulose over Eudragit and sodium alginate. But this method had advantages over other two i.e.Sodium carboxymethyl cellulose (polymer) is incorporated in a very small amount with highly effective output and mixture had to be maintained at 1000rpm rather than higher Rpms.\With the use of sodium alginate or Eudragit as polymer more time was required to prepare microspheres and more care was needed. Drug was equally distributed in the dosage form and by using this method high grade quality approved microsphere was obtained.

Material and Method:

Material:

Ibuprofen, Ethyl cellulose, Magnesium stearate, Tween 80, distilled water, Whatman filter paper, Mechanical stirrer, Electronic balance. All other chemical and reagent used in this study were of analytical grade.

Methods:

Pre-formulation tests of ibuprofen:

Bulk density:

50g of sample was added into the measuring cylinder of 250ml without compacting and disturbance. Apparent volume was measured designed as bulk volume. Bulk density wascalculated by using the given formula:

$$\text{Bulk density} = \frac{\text{weight}}{\text{bulk volume}}$$

Tapped density:

50g of sample was added into the measuring cylinder of 250ml and tapped until a constant volume was reached i.e. 600 taps.Measure the tapped volume and calculated the tapped density iby using the given formula:

$$\text{Tapped density} = \frac{\text{weight}}{\text{tapped volume}}$$

Hausner ratio and compressibility index:

Hausner ratio was determined by taking the ratio between the tapped density and bulk density.So it was measured by the following formula:

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Compressibility index was measured by the following formula:

$$\text{Compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Angle of repose:
A paper of known dimensions was taken and weighed accurately. The area of the paper was calculatedby the measured length and width. Then we calculated the grammage (weight per unitarea g/m^2) of the paper by the following formula:

$$\text{Grammage of paper} = \frac{\text{weight of paper}}{\text{area of paper}}$$

Afterwards, we took a funnel and adjusted it on the stand and placed the paper of which area was determined. Weighed 100g of powder and pour it in the funnel. We allowed the powder to flow so as to form the heap on paper. Measured the height of heap and encircles the area that heap covered. We cut the encircled area and weighed it precisely. Now we calculated the area of this circle by the following formula:

$$\text{Area of circle} = \frac{\text{weightofcircularpaper}}{\text{grammageofpaper}}$$

We calculated the radius of circle by using the following formula:

$$\text{Area} = \pi r^2$$

$$r = \sqrt{area\ of\ circle/\pi}$$

We calculated the angle of repose by the following formula:

$$\alpha = \tan^{-1}\left(\frac{\text{height}}{\text{radius}}\right)$$

Method to formulate the microspheres:
1g of ethyl cellulose was dissolved in 20ml of chloroform to form a homogenous polymer solution. Then 2g of ibuprofen was added to the polymer solution with a 0.01g of magnesium stearate and mixed thoroughly (solution 1). Then prepared another solution containing 0.01g of tween80 in 100ml of water (solution 2) was formed. Afterwards the polymer solution was added in solution 2, while stirring at 2000rpm to emulsify the added dispersion as fine droplets. The solvent, chloroform was then removed by evaporation during continuous stirring at room temperature for 3 hours to produce spherical microspheres. Here chloroform was used as polymer solvent, tween80 as the dispersing agent. During 3hrs stirring period, chloroform was completely removed by evaporation. The microspheres were collected by vacuum filtration and washed repeatedly and dried in room temperature over a night to get free flowing microspheres.

Post formulation test:
Microscopic Analysis:
A small amount of the sample was taken with the help of the stirrer and place on a clean slide.The slide was observed under optical microscope.

Drug loading capacity:
10mg of microspheres was dissolved in 10ml of chloroform. The concentration of drug in the solution was found with the help of spectrophotometer at wavelength 273nm. The solution was filtered, diluted suitably and the absorbance of resultant solutions was measured spectrophotometrically at 273nm

$$\text{Drug loading capacity} = \frac{\text{wt.of iboprofen in microsphere}}{\text{total wt.of drug}} \times 100$$

Drug Release:
The USP dissolution rate testing apparatus was employed to study the release of ibuprofen

microspheres using phosphate buffer PH 6.8 as a dissolution medium.200mg equivalent of ibuprofen containing microspheres was taken a dissolution test was being carried out at 50 rpm maintained at $37^0C \pm 0.5^0C$. 5ml of samples were withdrawn at specific time interval for 30 min. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at 221nm. The percentage of drug release at various time intervals was calculated and plotted against time.

Results:

Pre-formulation tests:

Bulk density:

Bulk density of ibuprofen came out to be 0.416g/ml as shown in table 2

Parameters	**Values**
Weight	50g
Bulk volume	120ml
Bulk density	0.416g/ml

Table 2: bulk density of ibuprofen

Tapped density:

Measured the tapped volume and the tapped density after 600 tapped came out to be 0.537g/ml.

Parameters	**Values**
Weight	50g
Tapped volume	93ml
Tapped density	0.537g/ml

Table 3: tapped density of ibuprofen

Hausner ratio and compressibility index:

The hausner ratio of ibuprofen powder came out to be 1.29 and the compressibility index of ibuprofen came out to be 22.5 which showed that the sample powder was passable. Result are tabulated in table 4.

Parameters	**Values**
Tapped density	0.537g/ml
Bulk density	0.416g/ml
Hausner ratio	1.29
Compressibility index	22.5

Table 4: Hausner ratio and compressibility index of ibuprofen

Angle of repose:

Angle of repose was calculated by determining different parameters such as area, length, width, mass, grammage of the paper and weight.

$$\alpha = \tan^{-1}\left(\frac{0.06}{0.06464}\right) = 42.96^{o}$$

The angle of repose came out to be 42.96^o which is passable according to the specification.

Post-formulation tests:

Drug loading capacity:

Table 5 shows us the results obtained during the determination of drug load capacity, while the figure 3 illustrating the relation between the absorbance and concentration.

Sr. no.	Concentration (µg/ml)	Absorbance
1	5	0.067
2	10	0.122
3	15	0.212
4	20	0.295
5	25	0.388
6	30	0.469
7	35	0.571

Table 5: drug loading capacity of ibuprofen microsphere

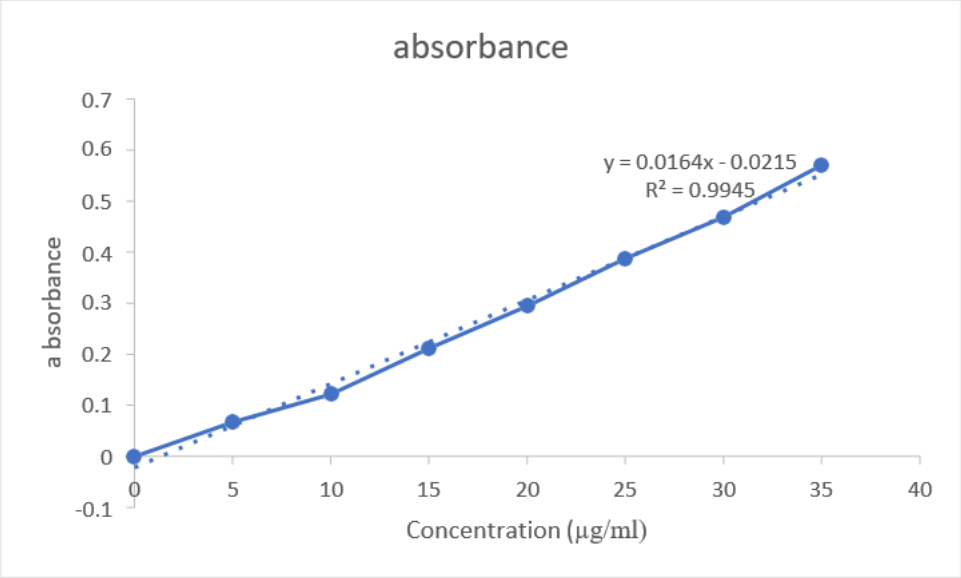

Figure 3: Graphical representation of absorbance Vs Concentration

Drug Release:

The results obtained after the determination of drug release is shown in table 6 and figure 4 represents therelation between percentage release and time.

Sr. no	Time (min)	Absorbance	%age release
1	30	0.01	2.045455
2	60	0.027	4.72028
3	90	0.039	6.608392
4	120	0.05	8.339161
5	180	0.0729	11.94231
6	240	0.09	14.63287
7	300	0.13	20.92657
8	360	0.169	27.06294
9	420	0.191	30.52448
10	480	0.217	34.61538

Table 6: Drug release profile of ibuprofen microsphere

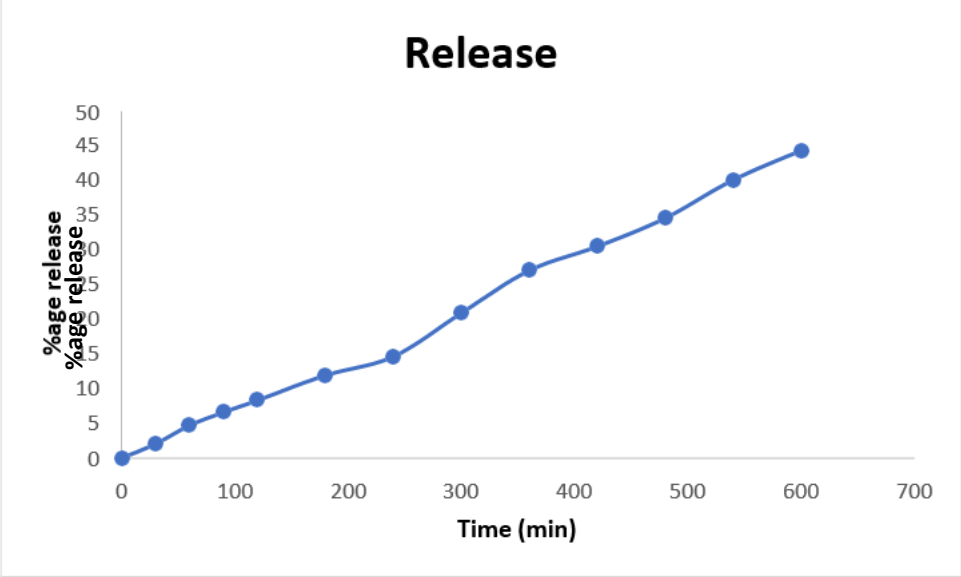

Figure 4: Graphical representation of drug release profile

Microscopic analysis of ibuprofen microsphere:

Figure 5: Microscopic analysis of ibuprofen microsphere

Discussion:

In this study, it was aimed to develop ibuprofen microspheres using water insoluble polymer (ethyl cellulose) as a carrier for oral administration to increase the period of the dosage form.In this process, uniform ibuprofen microspheres are produced. These microspheres were characterized for Loading capacity and percentage drug release. The formulation offered good characteristic properties. The technique also showed good loading efficiency. The micrometric parameters like angle of repose, bulk density and tapped density of ibuprofen raw material confirms better flow and packaging properties. Also showed good flow ability represents in terms of angle of repose, Compressibility index, and Hausner's ratio.The results are given in Table 2 and 3.

The microspheres were found to be discrete, spherical and free flowing. The percentageloading capacity was found to be in the range of 83%. The mean particle size of the various formulations was found to be in the range of 35-65mm.The results are given in Table 5 and figure 3.Microspheres prepared with ibuprofen and Ethyl cellulose in 1:2 ratio shown sustained drug release for a period 10 hours.The release data was given in table 6, Thus the drug release from microspheres was found be quite stable.

Conclusion:

The ethyl cellulose microspheres of ibuprofen were successfully formed by solvent evaporation method. Microspheres prepared with ibuprofen and Ethyl cellulose in 1:2 ratio shown sustained drug release for a period of 10 hours. This gave a hope to the possibility of single dose treatment for patients.

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