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Formulation development and characterization of ethyl cellulose microspheres of ibuprofen

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ABSTRACT

The main objective of this work was toinvestigate the possibility of obtaining a sustained release formulation of ibuprofen microspheres by using ethylcellulose in various drugs, polymer ratios (1:2, 1:1, 2:1).Microspheres are the novel drug delivery system (NDDS) as a controlled release dosage form to maintain relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAIDS) was formulated as microspheres by using ethylcellulose as carrier. These ethylcellulose microspheres were prepared by the solvent evaporation method. The prepared microspheres were subjected to various evaluation and invitro release studies. Highest percentage of loading was obtained by increasing the amount of ibuprofen with respect to polymer. The particle sizes of the prepared microspheres were determined by optical microscopy. The invitro release studies showed that ibuprofen microspheres of 1:2 ratios hadbetter sustained effect over a period of 10 hours.

Key words: Ibuprofen, Ethyl cellulose, Microspheres, NSAIDS

INTRODUCTION

In contrast to drug delivery system, the wordnovel is searching something out of necessity. Thedrug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance.[1] In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect , adverse effect decreases by lowering peak plasma concentration.[2]The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system.[3]Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level.[4]It has a particle size of (1-1000nm).[3]Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems

spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.4 Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.[5]

Ibuprofen is a non-steroidal anti-inflammatory drug, which possess analgesic and mild antipyretic action, because of its short half-life (1-3 hours) it was selected as model in this study.[6] Its activity is more than indomethacin, naproxen and other NSAIDS. Ibuprofen mediating the inflammation by acting on cyclooxygenase and it inhibit the lipoxygenase pathway, these decreases the production of leukotrienes by the leukocytes and the synovial cells. It also masks T cell suppressing the production of rheumatoid factors. Most frequent adverse effects occurring with ibuprofen are gastro intestinal disturbance; peptic ulceration and gastrointestinal bleeding have been reported. Hypersensitivity reaction, abnormalities of liver function including intestinal nephritis or the nephritic syndrome. Sustained drug delivery of ibuprofen will reduce these toxicities considerably by maintaining a low and constant level of drug in the blood. [7, 8]

MATERIALS AND METHODS

Material

Ibuprofen (Sun Pharma Baroda), Ethyl cellulose (SD fine chemicals Ltd. Mumbai, India), Dichloromethane (Rankem), Cyclohexane (Rankem), Tween 80 (Thomas baker Pvt. Limited), HPLC water (Rankem), HPLC grade methanol (Qualigens), Whatman filter paper , Mechanical stirr (Remi motor), double beam spectrophotometer (Systronic), Electronic balance (Vibra & Essae). All other chemical and reagent used in this study were of analytical grade.

Method

Calculated quantity of polymer was dissolved in 100ml of chloroform to form a homogenous polymer solution. Then calculated quantity of drug was added to the polymer solution and mixed thoroughly. The resulting mixture was then added in a thin stream of 200ml of aqueous mucilage of sodium CMC (0.5%) containing 1%(v/v) tween80, while stirring at 1000rpm 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, aqueous mucilage of sodium CMC as the microencapsulating vehicle, 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. By varying this drug: polymer ratio, three batches of microspheres were prepared.[9,10,11,12]

Table 1: Composition of Ibuprofen microspheres of ethyl cellulose

Batch code	Polymer: Drug ratio
M1	2 : 1
M2	1 : 1
M3	1 : 2

Physicochemical characterization of the microspheres:

Percentage yield

The driedmicrospheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula, [13]

Percentage yield = {The weight of microspheres / The weight of polymer + drug}*100

Drug content

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of phosphate buffer PH 7.4 then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 228nm. [9]

Drug loading and encapsulation efficiency
Drug loading and encapsulation efficiency was determined for all batches using the following formulas. Values are expressed as percentage. [13]

Drug loading = {Weight of drug in microspheres / Microspheres sample weight} * 100

Encapsulation efficiency = {Actual weight of drug in sample/ Theoretical weight of drug} * 100

Particle size analysis
Size distribution plays a very important role in determining the release characteristics of the microsphere. Particle size distribution analysis was done by optical microscopy method, using calibrated eye piece micrometer, nearly 200 particles were measured and the results were determined.[14]

***In-vitro* drug release**
The dissolution rate testing apparatus was employed to study the release of ibuprofen using phosphate buffer PH 7.4 as a dissolution medium.100mg equivalent of ibuprofen containing ethyl cellulose microspheres was filled in dissolution appratus and dissolution test was being carried out at 50 rpm maintained at $37^{o}C \pm 0.5^{o}C$. 5ml of sample were withdrawn at specific time interval for 10hours. The sample volume was replaced by an equal volume of fresh medium. The amount of drug release was analyzed at 220 nm using double beam spectrophotometer (Systronic). The same procedure was repeated for other formulations also. The percentage of drug release at various time intervals was calculated and plotted against time.[15,9]

RESULTS AND DISCUSSION

Percentage yield:
The percentage yield of three formulations was ranging from 68.70 to 86.10respectively (Table 2). This higher percentage yields indicates that this method was very useful for adoption in the formulation of ibuprofen microsphere.

Determination of drug content:
The results of the determination of microsphere drug content for various polymer : drug ratios are shown in table 2.From the three formulation M3 has the highest miligram of the drug content following by other formulations. Because it may be due to the highest amount of theoretical drug content and highest percentage yield in this ratio.

Table 2: Determination of drug content

Formulation code	Polymer/drug ratio	Theoretical drug content(mg)	Actual drug content(mg)	Percentage Yield
M1	2:1	500	343.5	68.70
M2	1:1	500	397.2	79.44
M3	1:2	1000	861.0	86.10

Drug loading and encapsulation efficiency:
The results of the variation in drug loading and encapsulation efficiency with polymer: ibuprofen ratio is shown in table 3. Higher percentage of loading was obtained by increasing the amount of ibuprofen with respect to ethyl cellulose. The encapsulation process was found to be good and 71.51 to 77.51 of the drug employed in the process were encapsulated by the microsphere. The percentage of encapsulation was higher (77.51%) in M1 formulation. This improved encapsulation efficiency simply by due to the greater proportion of polymer with respect to amount of drug.

Table 3: Drug loading (%) and encapsulation efficiency (%):

Formulation code	Polymer/drug ratio	Percentage of Formulation loading efficiency		Percentage of drug encapsulated
		Theoretical	Actual	
M1	2:1	35.3	32.10	77.51
M2	1:1	53.7	42.70	71.43
M3	1:2	67.1	63.45	73.54

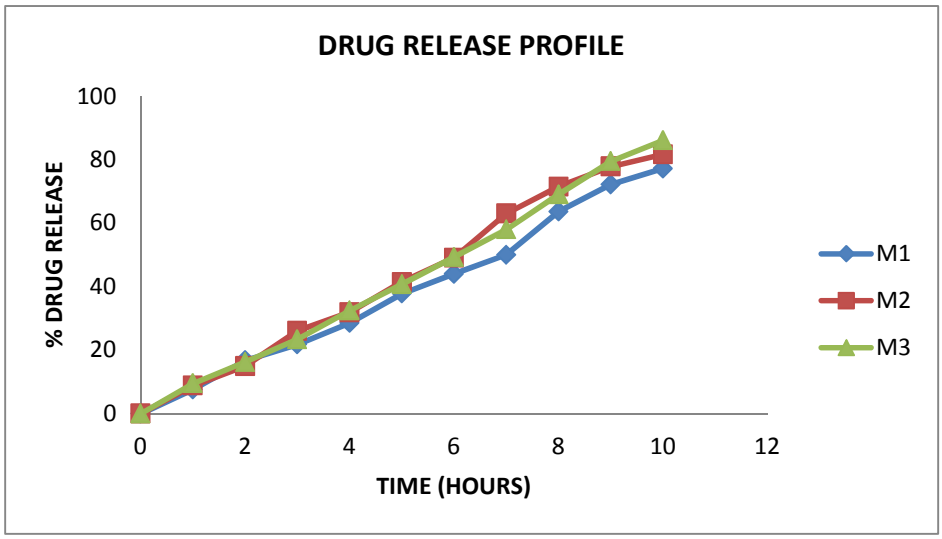
Particle size:
The particle size of ibuprofen loaded microsphere was analyzed by optical microscopy. All the batches of microspheres show uniform size distribution. The average particle size of ibuprofen loaded microspheres was found to be in the range of 221 to 357µm. As the polymer: drug ratio was increased, the microspheres size was also found to be increased (table 4).

Table 4:Particle size analysis

Batch code	Average particle size(µm)
M1	221.13
M2	341.27
M3	357.21

***In-vitro* drug release studies**
Microspheres of all batches had faster initial drug release approximately 25% within 15 minutes. Then the release was slow and sustained over 8 hours, depending upon the polymer: drug ratio. By the end of 8th hour the percentage of drug release was found to 77.27, 81.69 and 86.11 for M1, M2 and M3 formulation respectively (figure 1). The formulation F3 showed better sustained release at the end of the 8th hour as compared to other batches. This may be due to better loading, encapsulation efficiency and increased particle size as compared to other batches.

Fig 1;*In-vitro* drug release



CONCLUSION

The ethylcellulose microspheres of ibuprofen were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing ibuprofen loaded microspheres from its higher percentage yield. The formulation M3 has highest milligram of drug content followed by other formulations. The percentage of encapsulation of three formulations was found to be in the range of 71.43 to 77.51. Higher percentage of loading was obtained by increasing the amount of ibuprofen with respect to polymer. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The average particle size was found to be in the range of 221-357µm. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. The invitrodissolution studies showed that ibuprofen microspheres formulation M3 showed better sustained effect over a period of 10 hours than other formulations.

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