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Enteric Coated Beads Of Naproxen: Design, Development And Evaluation

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Abstract: When given orally to the patients, non steroidal anti inflammatory drugs (NSAIDS) can provoke mild to severe gastric irritation. Reduced gastrointestinal irritations caused by NSAIDS can be achieved by using enteric beads which are preferable to coated tablets or capsules. Enteric coated beads are prepared by coacervation technique. The method relies on the precipitation of the enteric polymer cellulose acetate phthalate (CAP), when their solutions in an aqueous alkaline media are dropped into an acidic environment. Studies were carried out to characterize the formulation such as angle of repose, drug entrapment, encapsulation efficiency and *in-vitro* release studies. *In-vitro* release studies showed that the enteric coated beads are suitable for further pharmaceutical manipulation (e.g. capsule filling). *In-vitro* release studies showed that drug release followed first order kinetics.

Keywords*:* Non steroidal anti inflammatory drug, Naproxen, CAP, enteric beads.

Introduction

Oral drug delivery is the most desirable and preferred method of administrating therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations mainly, because of patient acceptance, convenience, and the cost effective manufacturing process.

NSAID drugs having analgesic and anti-inflammatory effects are being widely administered orally in the treatment of mild to severe pain particularly for rheumatoid arthritis and osteo-arthritis patients. Tolerance or addiction to these drugs is not generally a problem with their continuous use in the treatment of pain or in the treatment of acute or chronic inflammatory states. However, these drugs generally have a higher potential for adverse side effects at the upper concentration of their effective dose range. A trend in NSAID development has been to improve therapeutic efficacy and reduce the severity of upper GI side effects through altering dosage forms of NSAIDS by modifying release of the formulations to optimize drug delivery. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered peak plasma concentration (1).

The non steroidal anti-inflammatory drugs like Ibuprofen and Naproxen have been widely prescribed by physicians. These drugs are in general tolerated well by most patients and provide an

effective means for control of pain and inflammatory processes, particularly for the rheumatoid arthritis and osteo-arthritis patients. Enteric coated resist the acid content of the stomach readily and dissolve in neutral fluids of the small intestine. Enteric coating results in different composition of respective gastric and intestinal environments with regard to pH and enzymatic properties. Most currently used enteric coatings are weak acids that remain undissociated in the low pH environment of the stomach that readily dissolves in the raise of the pH above 5.

Naproxen is used as analgesic and anti inflammatory to treat pain and inflammation caused by conditions such as arthritis, ankylosing, spondylitis, tendinitis, bursitis, gout, with a half life of 12-24 hours. However, most frequent adverse effects occuring with administration of Naproxen are gastro intestinal ulceration and bleeding (2). Enteric systems have several applications in pharmacy for both specific drugs and disease states. Enteric coated beads are those in which the drug is dispersed throughout the polymeric, matrix efforts some protection to the gastro intestinal mucosa.

Cellulose acetate phthalate is a white, hygroscopic, tasteless and odorless , free-flowing powder, granule, or flake. Cellulose Acetate Phthalate is used as an enteric coating on capsules or tablets so they don't dissolve until they reach the small intestine. Enteric coatings are selectively insoluble substances which will not dissolve in the acidic juices of the stomach, but they will dissolve in the higher pH (above pH 5.5) of the small intestine. Enteric coated tablets resist the action of the acidic stomach fluids and pass through it before the coating can dissolve thus protecting the gastric mucosa from the irritating effects of the ingredients in the tablets e.g. aspirin. The coating dissolves in the neutral or alkaline medium of the intestine and the active ingredients become available for absorption into the blood stream.

The aim of the present work is to coat the drug Naproxen by the enteric coating material cellulose acetate phthalate (CAP) by coacervation technique. The main goal still remains to solve the problem of NSAID-induced GI toxicity with its resultant morbidity and mortality and to obtain optimal therapeutic effect with least possible side effects (3). Enteric coating is formulated to prevent the formulations from gastric fluid in the stomach and release the drug component in the intestinal region or once it has passed into the duodenum, thereby minimizing the gastric irritation caused during prolonged treatment.

Materials And Methods

Materials Used

The following materials were used for the research work. The entire chemicals used were of best quality available. Naproxen (Caplin point laboratories, ltd .UNIT II, Gummidipoondi-601201), Cellulose acetate phthalate (Star scientific, erode-3), Methanol (Hi media laboratories PVT.LTD .mumbai-05), Concentrated hydrochloric acid, Citric acid and Sodium hydroxide (NICE chemicals pvt.ltd, cochin-24), Disodium hydrogen phosphate (Merck pvt. Ltd, Mumbai), Sodium bicarbonate (Thermo electron lls India pvt .ltd Mumbai-22), Sodium sulphate (Loba chemie Pvt, ltd, Mumbai-05)

Method Of Preparation Of Enteric Coated Beads

Both empty and drug containing beads are prepared by coacervation technique. Preparation procedure relies on change in solubility of CAP with change in pH. An appropriate amount of drug was weighed according to drug polymer ratio as 1:2, 1:3, 1:4, and 1:5.Calculated quantity of CAP was dispersed in alkaline solution (5%w/v of Sodium Bicarbonate). The suspension was then added with the required quantity of the drug with continuous stirring (Table 1). The resulting suspension was added through the needle to 20% Sodium Sulphate solution with constant mechanical stirring, and the pH was maintained in sodium sulphate by adding citric acid. (pH 4)

The pH difference between the drug polymer suspension and sodium sulphate citric acid solution causes precipitation of the polymer CAP leading to the formation of spherical beads that include the drug Naproxen.(4). It is left for curing till it gets hardened and is washed with acidified aqueous solution to remove sodium sulphate. The washed CAP enteric coated Naproxen beads are then filtered and dried for further use. Thus most currently used enteric coatings are weak acids that remain undissociated in the low pH environment of the stomach, but readily ionize when pH rises to above 5. (5).

Table 1: Content of drug polymer suspension

Formulation	Drug polymer ratio	Suspension	
		Drug	Polymer
F1	1:2	1.25gm	2.5gms
F2	1:3	1.25gms	3.75gms
F3	1:4	1.25gms	5gms
F4	1:5	1.25gms	6.25gms

Evaluation Of Enteric Coated Beads Of Naproxen

The flow property was investigated by measuring the angle of repose of drug loaded enteric coated beads using funnel method. The funnel was fixed at 1cm above the horizontal flat surface. The beads were allowed to pass through the funnel till the apex of the conical pipe just touches the tip of the beads and the angle of repose was determined by: $\theta = \tan^{-1}H/R$ (6). The particle size distribution analysis was carried out by using sieve method by taking 2gms of enteric coated beads and passed through sieves of No: 8,10,12,16. The fractions retained on each sieve were collected and weighed. The average diameter of the particles was calculated for all the formulations F_1-F_4. The bulk density of the beads was determined by using 10ml graduated cylinder. The accurately weighed quantity of enteric coated beads was added to the cylinder and tapped nine times. The volume is noted and bulk density is calculated by using the formula: $\Upsilon = M/V$. The amount of drug encapsulated was determined by dissolving 100 mg of the prepared beads in 3 ml of methanol and volume was made up to 100 ml with buffer solution of pH 6.8 in a 100 ml standard flask. From this, 1ml of solution was withdrawn and made up to 10 ml. This solution was analyzed for the drug content by using UV Spectrophotometer at 230.2 nm. From the standard graph of Naproxen the drug content was calculated.

Morphology

Formation of good quality beads with a spherical shape depends mainly on the viscosity of the drug polymer ratio. For further characterization of the shape and surface of the enteric coated beads photographs were taken using Scanning Electron Microscope (Hitachi, S-3600, N) at 15Kv.The sample is placed in an ion charging effect of the electron beam during SEM observation. This was done with ion sputter coating unit prior to examination. Samples were gold coated under vacuum (Bio RAD micro science division, sc 502) to render them electrically conductive. Then the samples are placed in Scanning Electron Microscope (Model No: Hitachi, S-3600, N) for SEM observation and the photo micrographs are taken at different magnificent (Fig 3 & Fig 4) .

Fourier Transforms Infrared Spectroscopic Analysis (FTIR):

Drug polymer interactions were studied by FT-IR spectroscopy.1-2 mg of the drug Naproxen, polymer and drug loaded enteric coated beads samples were weighed individually and mixed properly with potassium bromide to obtain a uniform mixture. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 450-4000 cm^{-1} was recorded taking air as the reference and compared to study any interference (7), (8) .

Detrmination Of Drug Content

Naproxen content in the micro beads was established by UV spectrophotometric method. Accurately weighed 100 mg of enteric coated beads were suspended in 3 ml of methanol and 100 ml of phosphate buffer pH 6.8. The solution was filtered after suitable dilution. Naproxen content in the filtrate was analyzed at 230.2 nm using UV-Visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor we get the percentage of actual drug encapsulated in enteric coated beads. The drug entrapment efficiency was determined using the following relationship.

%drug entrapment efficiency=Actual Drug content/Theoretical drug content×100.

***In-Vitro* Drug Release Studies**

The dissolution testing of enteric coated formulation was carried out according to USP 27, by adopting Method B (USP) in pH 1.2 and pH 6.8 buffers. The acid Stage was performed using 900 ml

of 0.1 M hydrochloric acid placed in a USP dissolution bath equilibrated to a temperature of 37± 0.5 °C. The paddle stirring rate was set at 100 rpm. Three capsules filled with the enteric coated beads 86.5mg each (equivalent to 250 mg) were introduced into the rotating basket and the apparatus was run for 2 hours. At scheduled time intervals samples were withdrawn and replaced with the fresh medium. After the operation outlined above, was completed the agitation was stopped and the medium was replaced for the buffer stage to commence.

The Buffer Stage consisted of a phosphate buffer of pH 6.8. The apparatus was operated for a further 6 h. At the regular time intervals, an aliquot of the fluid was withdrawn and the samples were assayed spectrophotometrically at 230.2 nm. The release profiles of Naproxen from enteric coated beads were examined in simulated gastric fluid and in phosphate buffer of pH 6.8.

In order to understand the mechanism and kinetics of drug release data, in vitro dissolution study was analyzed using various kinetic equations as zero order, first order, Higuchi model, in order to authenticate the release model, dissolution data can be further analyzed by Korsmeyer and Peppas equation $M_t/M_\infty=Kt^n$. (9)

Results And Discussion

Evaluation Of Enteric Coated Beads

The rheological parameters like angle of repose of all the enteric coated beads showed better flow and packing properties. All the formulations showed excellent flow ability, as represented in terms of angle of repose (<40 ^{0}C). The batches prepared with coating polymer shows good flow ability due to formation of smooth layer on the surface of the enteric coated beads. The particle size for the different formulation (F1-F4) ranged from 2000µm-2380µm.Increase in polymer concentration increases the mean particle size of the beads. This is due to the increase in viscosity, which in turn increase the droplet size during addition of the polymer solution to the cross-linking agent solution. Particle size also increases by increasing the drug load. When drug is included the mean diameter of the bead increases and the particle size distribution become narrower. When increase in the mean diameter is obtained for the preparations it may be due to higher viscosity (F4). The bulk and tapped density of the enteric coated beads were also determined. It shows good acceptable range and found to have higher pack ability. The improvements of micromeretic properties suggest that prepared enteric coated beads can be handled.

The percentage amount of drug that was incorporated into the beads depends upon the drug: polymer ratio. The drug content determination studies confirmed that the drug was encapsulated in all the formulations (F1 to F4) was in the range of (91.20±0.78 to 93.70±0.65). High encapsulation efficiency of Naproxen was achieved with this method, which may be due to the fact that this drug is in acidic media and doesn't partition to the citric acid solution during the preparation.

Entrapment efficiency revealed the capability of giving maximum drug loading, which in turn depends on the drug polymer ratio. High encapsulation efficiency levels of naproxen depend on the acidic media of the solution. The drug entrapment efficiency decreased progressively with increasing cellulose acetate phthalate concentration resulted in the formation of large enteric coated beads entrapping lesser amounts of the drug. It was found that when the concentration of the polymer increases the dissolution rate of the drug decreases. Among different concentration of the drug polymer ratio the formulation F1 has good entrapment efficiency than the other formulations due to the low viscosity (**Table 2).**

Table 2: Values of Angle of repose, Mean Particle Size, Bulk Density and Drug entrapment efficiency of the prepared enteric coated beads of Naproxen

S.No	Formulation	Angle of repose	Mean particle size (µm)	Bulk densities values	Drug entrapment efficiency (%)
1.	F1	$27^o38'$	2000	0.492±0.009	93.70±0.65
2.	F2	$29^o96'$	2250	0.524±0.015	92.92±0.89
3.	F3	$26^o56'$	2300	0.458±0.018	90.84±0.86
4.	F4	$32^o76'$	2380	0.514±0.006	91.20±0.78

FIG 1 BEADS SHOWING IRREGULAR MORPHOLOGY

FIG 2 BEADS SHOWING SMOOTH MORPHOLOGY

FIG-3 TRANSVERSE SECTION OF THE ENTERIC COATED BEAD OF NAPROXEN AT 500X MAGNIFICATION

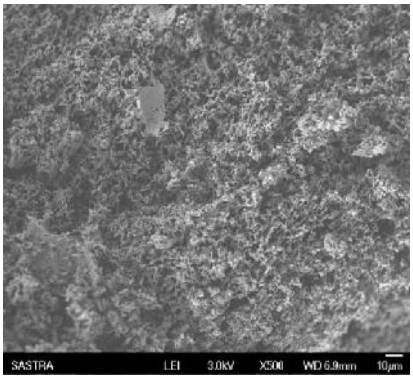
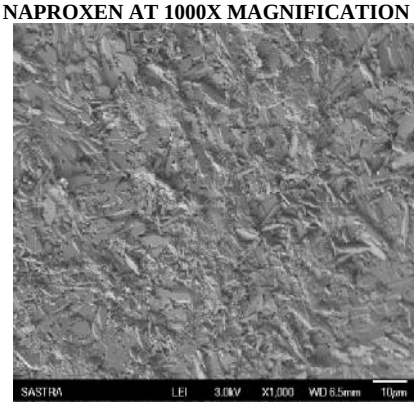


FIG-4 TRANSVERSE SECTION OF THE ENTERIC COATED BEAD OF NAPROXEN AT 1000X MAGNIFICATION



Morphology:

The SEM photomicrographs of the enteric coated beads were prepared by using the coacervation technique.(Fig 1 & Fig 2) .The photomicrographs of the prepared enteric coated beads of the formulation F1 (1:2) were almost spherical in shape and had a smooth surface (Fig 3 & Fig 4). The enteric coated beads revealed smooth and almost discontinuous film on to the spherical surface of the beads. The Trans section of the bead shows that the drug and the polymer are equally distributed. The formation of pores on the surface of the enteric coated beads after dissolution indicated that the drug release from the beads is possibly by the diffusion. The decrease in size of beads after dissolution revealed that the release of drug was not only by diffusion but also by surface erosion of polymers from the enteric coated beads. There was no sign of coating material on the surface of enteric coated beads after dissolution in phosphate buffer (pH 6.8). While increasing the polymer concentration the beads are not in spherical shape F_3 andF_4 formulation showed almost an irregular shape.

Fourier Transform Infrared Spectroscopic Analysis (FT-IR):

The FTIR spectroscopy was used to identify the possibility of any interaction between the formulation components. There was no significant difference in the FTIR spectra of the drug and drug-loaded beads when compared to the spectra of individual components. The characteristic C = N and S = O stretching band of drug remained unchanged in case of the drug-loaded micro beads. Also the peaks corresponding to stretching, C = C stretching in aromatic ring, C – O of -OCH3 and C – H bending of CH2, CH3 were retained in the FTIR.

Spectrum of the drug loaded enteric coated beads reflecting the identity features of the Naproxen. This finding indicates that possibly there was no chemical interaction between the drug and polymer backbone and the drug entrapment and modulation of release is due to the physical entanglement only.

Fig 5: Graph showing the *in-vitro* drug release studies of naproxen from the enteric coated beads

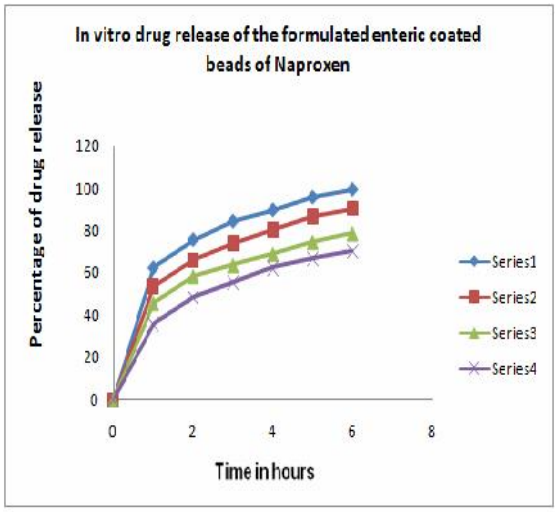


Table-3: Kinetics of drug release of Enteric coated beads of Naproxen

S. No	Formulation Code	Zero Order	First Order	Higuchi's Model	Peppa's Model	
					n	R2
1.	**F1**	0.9756	**0.9930**	0.9950	0.2600	**0.9991**
2.	**F2**	0.9824	**0.9983**	0.9978	0.2921	**0.9997**
3.	**F3**	0.9797	**0.9963**	0.9951	0.2962	**0.9971**
4.	**F4**	0.9737	**0.9932**	0.9942	0.3774	**0.9970**

In-Vitro Drug Release Studies

The release of naproxen was studied in 0.1 M HCL (pH 1.2) and phosphate buffer (pH 6.8). Since the CAP polymers are insoluble in acidic medium, very little amount of drug was released at the pH 1.2 compared to that in phosphate buffer (pH 6.8). Another cause of low drug release in the acidic medium is that the drug is a weak acid and therefore, it will remain unionized in the same medium. On increasing the amount of polymers there was a significant decrease in the cumulative drug release in both dissolution media (Fig 5).

The *in-vitro* dissolution data were analyzed by using different kinetic models in order to find out the n-value, which describes the drug release mechanism. The values of correlations were calculated and were found to be more linear for first order release as compared to zero order. The kinetic data was best fitted to Korsmeyer and peppa's model and good regression co-efficient ranged between n=0.260 to 0.377 (Table 3).

Conclusion

The present study indicates that the preparation of enteric coated beads was based on coacervation technique by using CAP which can be an effective technique of encapsulating Naproxen. Beads with high drug loading and a most monos disperse particle size distributed could be prepared. The beads obtained were smooth, spherical and suitable to be incorporated into capsules, while the *in-vitro* release profiles confirmed their gastro resistance, thus allowing pH-dependent release of Naproxen in the gastro intestinal tract. The application of mathematical models and a fitting curve to the experimental data from the release studies showed that the dissolution of the Naproxen contained in cellulose acetate phthalate matrices follows a first order release mechanism. Finally, the main advantages of this simple and mild technique are the one step production method, since it does not need a coating process, the absence of organic solvents and the strict use of non-toxic materials.

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