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Formulation and Evaluation of Amoxicillin Nanoparticles

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ABSTRACT

The present study has been undertaken to apply the concept of nanoparticulate mucopenetrating drug delivery system for complete eradication of Helicobacter pylori (H. pylori), colonised deep into the gastric lining. Most of the existing drug delivery systems have failed on account of either improper mucoadhesion or mucopenetration and no dosage form with dual activity of adhesion and penetration has been designed till date for treating H. pylori-induced disorders. In the present study, novel Eudragit nanoparticles of amoxicillin have been designed and optimized for various variables such as pH and mixing ratio of polymers, concentration of polymers, drug and surfactant. Various studies like particle size, surface charge, percentage drug entrapment, in-vitro mucoadhesion The optimized FITC labelled eudragit nanoparticles have shown comparative low in-vitro mucoadhesion with respect to plain eudragit nanoparticles, but excellent much penetration and localization as observed with increased fluorescence in gastric mucosa continuously over 6 hours, which clinically can help in eradication of H. pylori.

INTRODUCTION –

Sustained formulation has been widely developed and marketed over the past decades under various terms such as sustained release, prolonged release, time release, prolonged release, timed release, or other similar names that are often ill-defined and misleading Furthermore, these formulations represents little improvement in clinical efficacy of the drug over conventional dosage form. Rather their success attaints compliance. Despite the widespread use of controlled or sustained-release products for every class of drugs in the market, no manufacturers have claimed the therapeutic superiority of their controlled or sustained-release formulations over the existing conventional tablet or capsule form of the drug. More recently, a number of novel drug delivery systems that use unique concepts have been studied intensively. Some of the strategies include targeted delivery, self-regulated release, biofeedback mechanism and drug attached to biological carriers. The usefulness of these and other novel drug delivery concepts will certainly be demonstrated in the near future, with their successful application to currently available as well as newly developed therapeutic agents. Sustained release formulations can be designed for any route of administration. The oral route remains most common although the use of implant and transdermal routes is expanding. Traditionally, implants have been used for long-term delivery of drugs such as for hormone replacement therapy. This method remains useful even today in products such as contraceptive which is effective for five years of continuous therapy. Considering the tremendous advantage in the duration of efficacy from the implant formulation future applications of this approach could be explored for other drug as well. Most of the conventional antibiotics have a shorter half-life, which requires frequent dosing and thus reduces patient compliance nanoparticle are the carriers which make the drug more stable at acidic environment and protect its metabolism and some modification in the dosage form make it a career for sustain release. The release of antibiotics in causes several implications in which one of the major is erosion of gastric mucosa and ulceration. To prevent this some proton pump inhibitors can also be given with amoxicillin the present system is designed in a manner to deliver both the drugs in a system which delivers the drug in alkaline pH and prevents its degradation in acidic pH i.e. in stomach, thus minimizing their side effects and also make it a system for sustain release which increases patient compliance. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation in the harsh environment of gastrointestinal tract. Particles in the Nano size range

are absorbed intact by the intestinal epithelium, especially via payer's patches travels to sites such as the liver. Some of the potential advantage of Nanoparticulate system include protect the encapsulated drug from harsh gastric environments, Submicron size and large specific surface area favour their absorption compared to other large carrier's improved bioavailability as the particles in the Nano size range are efficient in crossing permeability Carrier's, have better patient compliance, Drug loading is relatively high, Prolongation of the residence time of drugs in the intestine, site specific and prolonged delivery of the selected drug, Minimize dose frequency, Reduced side effects.

MATERIAL AND METHOD –

MATERIAL: The sample of Amoxicillin was obtained from Ranbaxy Pvt. Ltd Gurgaon, HPMC K4M Burgoyne Burbidge's and Co., Mumbai, Eudragit RS100 Ranbaxy Pvt Ltd Gurgaon, N-hexane Ranbaxy Pvt Ltd Gurgaon, Span 80 LobaChemiePvt. Ltd., Mumbai, Acetone Merck Ltd., Mumbai, and other solvents used of analytical grade provided by ITM College of Pharmacy and Research Gida Gorakhpur.

Method:

Amoxicillin trihydrate nanoparticles were formulated using solvent evaporation technique, using Eudragit RS100 as matrix polymer. Eudragit was dissolved in required quantity of acetone, the HPMC K4M and drug were dispersed with the polymer solution. The dispersed content was placed drop wise in mineral oil containing span80 maintained at 40^0C while stirring at 750±50 rpm. The solvent, acetone was then removed by continuously stirring at room temperature for three hours to produce spherical nanoparticles than separated from mineral oil by filtration through Whatmann filter paper, the nanoparticles were collected and washed three times with n-hexane and dried using vacuum filtration. The product was then air-dried to obtain nanoparticles.

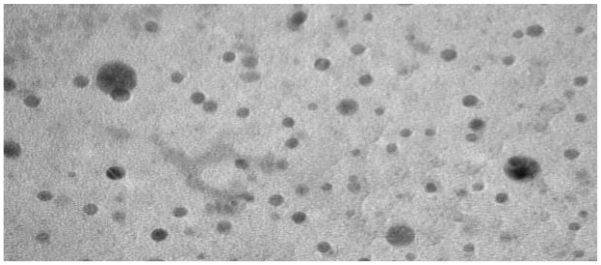
S.no	Batch code	Eudragit(mg)	Acetone (ml)	Hpmc K4M (W/V)	Mineral oil (ml)	Span 80 (w/v)
1	AMN1	100	35	0.5	34	1%
2	AMN2	150	35	0.5	40	2%
3	AMN3	200	35	1.0	40	2%
4	AMN4	250	40	1.0	40	2%
5	AMN5	300	40	1.5	40	2%
6	AMN6	350	40	1.5	40	2%
7	AMN7	400	40	1.5	40	2%

CHARACTERIZATION OF NANOPARTICLES:

1. Particle size and morphology:

Particle size and size distribution are the most important characteristics nanoparticles system. They determine the in vivo distribution, biological fate, toxicity and targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and the stability of nanoparticles. Many studies have demonstrated than the nanoparticles of sub-micron size have a number of advantages over micro particles as a drug delivery system. Generally, nanoparticles have relatively higher intracellular uptake compared to microparticles and are available to a wider range of biological targets due to their small size and relative mobility. Tween 80 coated nanoparticles have been shown to cross the blood-brain barrier in some cell lines, only submicron nanoparticles can be taken up efficiently but not the larger size microparticles. Drug release is affected by particle size. Smaller particles have a larger surface area, therefore, most of the drug-associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allows more drug to be encapsulate diffuse out smaller particles also have a greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability. The shape and surface characterization of nanoparticles were observed under a Scanning Electron Microscope (ZEOL

JSM-5610). The nanoparticles were mounted directly on the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr) and photographed.



2. Determination of drug content:

Accurately weighed 100mg nanoparticles, were crushed in glass mortar and pestle and powder nanoparticles were suspended in 100ml of 0.1 N HCL After 12 hours the solution was filtered and the filtrate was analysed for the drug content using a UV-Visible spectrophotometer. The drug content results profile of all formulations was mentioned in the table.

S.NO	Batch Code	Drug Content
1	AMN1	59.25 ±0.13
2	AMN2	62.34± 0.09
3	AMN3	65.33± 0.11
4	AMN4	64.13 ± 0.12
5	AMN5	61.34 ± 0.13
6	AMN6	59.24 ± 0.09
7	AMN7	57.34± 0.15

Determination of the drug content and particle size of prepared Eudragit nanoparticle

3. Encapsulation efficiency:

Encapsulation efficiency was calculated using the following formula given below-

Encapsulation efficiency = Estimated drug content/theoretical drug content ×100

4. Kinetics of drug release:

In order to understand the mechanism and kinetic of drug release, the drug release data of the in vitro dissolution study were analysed with various kinetic model like zero order, first order, Higuchi's Peppas and Coefficient of correlation (r) values were calculated for the liner curves by regression analysis.

5. Stability studies for best formulation:

The stability study was carried out using the batch AMN3. The stability of the drug-loaded nanoparticles was evaluated in terms of its drug content. The nanoparticle formulation was incubated at 4^0C room temperature, 45^0C for one month. The amount of drug was detected UV Spectrophotometrically at 285 nm. The stability study result of the best formulation was mentioned in the table.

S.NO	TIME	AMN3 FORMULATION		
		4 ± 2^0C	25 ± 2^0C	45 ± 2^0C
1	0	**100**	**100**	**100**
2	1	**95.56**	**97.43**	**94.75**
3	2	**97.54**	**95.56**	**93.54**
4	3	**93.42**	**94.32**	**92.34**
5	4	**92.65**	**93.65**	**88.86**

Stability studies of prepared best formulation of Eudragit Nanoparticles Containing Amoxicillin

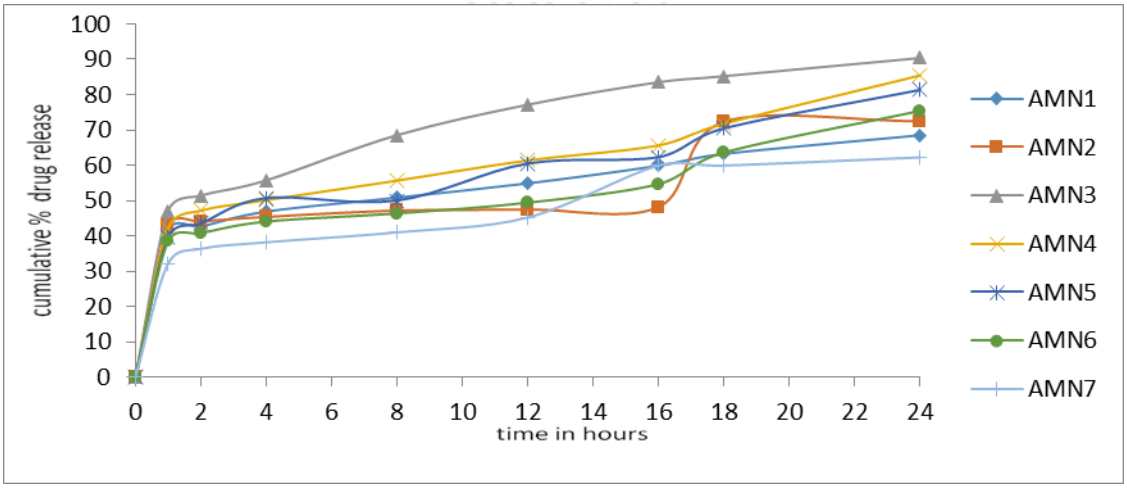
6. In-vitro dissolution studies:

Dissolution studies were carried out for all the formulations, employing the USP XXIII apparatus (Basket method) at 37 ± 0.5^0C rotated at a constant speed of 50 rpm using 0.1N HCL as the dissolution medium. A sample of microspheres equivalent to 100mg of amoxicillin trihydrate was used in each test. An aliquot of the sample was periodically drawn at suitable time intervals and the volumes were replaced with fresh dissolution medium at suitable time intervals and the

volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analysed Spectrophotometrically at 254 nm.

S.NO	TIME (In hours)	CUMULATIVE % DRUG RELEASE						
		AMN1	AMN2	AMN3	AMN4	AMN5	AMN6	AMN7
1	0	0	0	0	0	0	0	0
2	1	41.58	42.8	47.04	42.18	39.72	38.52	32.24
3	2	42.7	44.1	51.44	47.18	43.56	40.8	36.41
4	4	46.92	45.4	55.76	50.16	50.76	44.1	38.24
5	8	50.88	47.2	68.52	55.68	50.04	46.4	41.06
6	12	54.92	47.5	77.16	61.38	60.52	49.44	45.24
7	16	59.88	48.2	83.52	65.64	62.34	54.71	49.96
8	18	63.24	72.3	85.22	71.76	70.44	63.6	59.96
9	24	68.52	72.5	90.36	85.44	81.36	75.43	62.24

In vitro drug release studies of prepared Eudragit Nanoparticles



In vitro drug release

CONCLUSION:

The ratio of drug and polymer concentration 1:2 was found to be ideal. At the 24th hour, the maximum amount of drug was released. As amoxicillin has a short biological half-life, it was used in the controlled released formulation. The prepared nanoparticles release the drug in a controlled manner and the polymer used was nontoxic, biocompatible and freely available and act as a good carrier of the therapeutic agents. The forgoing show that Nanoparticulate systems have great potential, being able to convert poorly soluble, poorly absorbed and labile biologically active substances into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interaction and particle engineering is still required. Further advance is needed in order to turn the concept of nanoparticle technology into a realistic particle application as the further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system. Oral route is the most popular and convenient route for various drugs. Oral route generally considers an ideal drug delivery system that will possess two main properties that is it should be in a single dose for prolonging action and it should be deliver the active drug directly to the target site. These considerations have led to the development of a controlled or sustained delivery system. An ideal dosage form is one which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment, which is possible through administration of conventional dosage form offers no control over drug delivery, leading to fluctuation in plasma drug level. These have a disadvantage of a release all or nothing emptying process while the multiple unit particulate system passes through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation, this gave birth to oral controlled and sustained drug delivery and led to development of gastro retentive nanoparticles.

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