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Research article

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Research on formulation and development of amoxicillin microspheres by using spray drying technique

Ruchi Goyal*, Dr. Mayank Bansal, Vijay Sharma, Vimal Kumawat

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur (Rajasthan) India

*Corresponding Author: Ruchi Goyal

Email id: ruchigoyal95@gmail.com

ABSTRACT

The aim of the current investigation is to design oral once daily modified release dosage forms of amoxicillin trihydrate for treatment of H. Pylori infection, which release the drug for 24 hours and match with theoretical drug release profile. The tablets and capsules were prepared by the different method using different polymers in different concentrations. The interference of the polymers was ruled out by FT-IR spectroscopy studies. The powder-blends of tablets and drug were evaluated for their physical properties like angle of repose, bulk density, compressibility index, and Hausner ratio and found to be satisfactory. The manufactured tablets were evaluated for in process and finished product quality control tests including appearance, Swelling study, Drug entrapment efficiency, mucoadhesive of microsphere, Particle size analysis, drug content, and in vitro drug release. All formulations showed appearance, thickness, weight variation, hardness, friability and drug content in specified limit. All formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The formulated amoxicillin trihydrate tablets followed zero order release kinetics and Higuchi diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 24 hours. Formulations were subjected to short term stability studies as per ICH guidelines and were found stable. Microsphere formulations 8 were evaluated for weight uniformity, drug content and in vitro drug release.

Keywords: Amoxicillin, Antibiotic, Chitosan, Pharmacokinetic, in-vitro release.

INTRODUCTION

Amoxicillin an acid stable, semisynthetic drug belongs to a class of antibiotics called the Penicillin's (- lactam antibiotics). It is shown to be effective against a wide range of infections caused by wide range of Gram -positive and Gram- negative bacteria in both human and animals.

It is a congener of ampicillin (a semi-synthetic amino- penicillin) differing from the

parent drug only by hydroxylation of the phenyl side chain.

It has found a niche in the treatment of ampicillin-responsive infection infections after oral administration⁴⁻⁶. Chemically amoxicillin (2S, 5R, 6R) 6[[[(2R) 2Amino2(4hydroxyphenyl) acetyl] amino] 3,3dimethyl-7-oxo-4-thia-1-aza-bicyclo [3.2.0] heptane-2carboxylic acid.

PHYSICOCHEMICAL PROPERTIES

Amoxicillin is white or almost white (amoxicillin trihydrate-off white crystalline, and amoxicillin-sodium white or slight pink, amorphous, very hygroscopic) powders, with slight sulphurous odour, compatible with citrate, phosphate and borate buffers [7-9, 25]. Amoxicillin sodium is very soluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in acetone, while Amoxicillin trihydrate is slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Degradation of amoxicillin trihydrate as well as sodium, in sealed and open containers were found to show two step degradation at various temperatures. Under controlled humidity conditions, both the amoxicillin trihydrate and amoxicillin sodium showed first order degradation.

Literature data indicated that amoxicillin in dilute aqueous solution, was found to follow first order or pseudo first order degradation rate at constant pH with a minimum rate at about pH 6. Amoxicillin degradation was subject to catalysis by phosphate and citrate buffers with a 10-fold increase in rate with phosphate. Increasing ionic strength was reported to have positive effect on degradation rate in alkali and a negative effect in acid.

At higher concentration amoxicillin gave non first order degradation kinetics, indicative of dimerization reaction and the rate of dimerization of amoxicillin at pH 9 is greater than that of other aminopenicillins. Degradation of amoxicillin (sodium salt) at higher concentration became faster in the presence of carbohydrates (dextrose, dextran, and sorbitol) and alcohols. Amoxicillin showed a pH dependent stability with the stability increasing with decrease in pH 26. The acid-base catalysis was seemed to be the mechanism of degradation of amoxicillin in buffered solutions²⁵. Amoxicillin was reported with pKa values of 2.67, 7.11 and 9.55 at 37°C^{26, 27} found to have the lowest solubility at a pH range of 4 to 6²⁸. The relative solubility (the pH-apparent solubility profile) of amphoteric penicillin (amoxicillin) was determined under physiological temperature conditions for

amoxicillin and the results indicated U-shaped pH-solubility curve, with the minimum solubility at the pH near the isoelectric point.

PHARMACOLOGY

Amoxicillin is bactericidal against susceptible micro-organisms through the inhibition of biosynthesis of cell wall mucopeptide during bacterial multiplication. It acts by binding to penicillin-binding protein 1A (PBP-1A) located inside the bacterial cell wall. The penicillin's (amoxicillin), acylate the penicillin-sensitive transpeptidase C-terminal domain by opening the lactam ring causing inactivation of the enzyme, prevents the formation of a cross-link of two linear peptidoglycan strands, inhibiting the third and last stage of bacterial cell wall synthesis, which is necessary for cell division and cell shape and other essential processes; and thus, the lethality of penicillin for bacteria involves both lytic and non-lytic mechanisms. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that amoxicillin interferes with an autolysin inhibitor. The imperfect cell wall synthesis makes bacterial cells to absorb water by osmosis; as gram positive & gram-negative bacteria have 10-30 & 3-5 times intracellular osmotic pressure than external environment. Amoxicillin is more effective against gram positive than gram negative micro-organisms and it demonstrates greater efficacy to penicillin, penicillin V and comparable to other antibiotics, e.g. ampicillin, azithromycin, clarithromycin cefuroxime and doxycycline, in treatment of various infections/diseases.

In the past decade, amoxicillin has been reported to be useful in the management of many indications and is used to treat infections of the middle ear (otitis media), tonsils (tonsillitis & tonsillopharyngitis), throat, larynx (laryngitis), pharynx (pharyngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract (UTI), skin and to treat gonorrhoea. Published reports also suggest amoxicillin as a potential candidate in treatment of Chlamydia trachomatis, typhoid fever, early Lyme disease, erythema migrans & erythema migrans borreliosis, mucopurulent cervicitis, acute maxillary sinusitis, gastritis & peptic ulcers and meningitis conditions. Recently

American Heart Association (AHA), American Dental Association (ADA) and new recommendation by American Academy of Orthopaedic Surgeons (AAOS) changed prophylaxis protocols suggested that it can be used as prophylaxis against bacterial

endocarditis, in patients with prosthetic joint replacements and in dentistry. Amoxicillin is susceptible to degradation by β -lactamase-producing bacteria, and so may be given with β -lactamase inhibitor such as clavulanic acid.

PHARMACOKINETICS

Amoxicillin is well absorbed (at different rate and extent from various regions of gut) from GIT. It enjoys widespread clinical use, not only because of its broad antibacterial.

- Oral bioavailability : 95 % by oral route
- Protein binding : 20 %
- Volume of distribution (V/ F) : 0.2-0.4 L/kg
- Half- life : 60 min (average)
- Route of administration : Especially oral

DRUG INTERACTIONS

Food Drug Interactions

Fatty meal significantly interferes with amoxicillin, the time above MIC ($T > MIC$) was prolonged by administration with food. Mean unbound $T > MIC$ of 0.06 $\mu\text{g/ml}$ (minimum required for the inhibition of *S. pyogenes*) increased from 11.0 hours under fasting conditions to 12.2 hours with a low-fat meal and 14.6 hours with a high-fat meal.

Drug Drug Interactions

- **Clavulanic acid/ Potassium clavulanate:** Clavulanic acid (β - lactamase inhibitor) increases the effect of amoxicillin and inhibits the development of resistant in β -lactamase producing micro-organisms.
- **Clarithromycin and Lansoprazole:** Clinical trials involving the use of combination therapies (e.g. triple therapy in combination with clarithromycin and lansoprazole, or double with lansoprazole alone against *H. pylori*-related duodenal ulcer disease) no adverse effect peculiar to these combinations were observed.
- **Probenecid:** Concurrent amoxicillin use with this product or other inhibitors of the renal acid secretory system increases and prolongs blood amoxicillin concentrations.

MATERIAL

Amoxicillin was received from DSM Anti-infective India Limited, India and other excipient

received from Oxford laboratory, Loba. Chemicals Bombay Becta Laboratories Surat Qualigens Fine Chemical

Preparation of microsphere

Dissolution of polymer in a suitable organic solvent. Ex. Dichloromethane, acetone Dispersion of drug in the polymer solution. Under high homogenization speed. Atomization of dispersion in a stream of hot air Formation of small droplets due to atomization Solvent evaporation instantaneously. Formation of microspheres in size range of 1-100 μ Separation of microparticles from the hot air by means of cyclone separator. Vacuum drying is used to remove traces of solvent.

EVALUATION PARAMETER AND RESULTS

Determination of λ_{max}

The pure drug amoxicillin was scanned by UV Spectrophotometer at 200-400nm to determine λ_{max} . The peak was observed at 228nm for amoxicillin microsphere in 1.2 pH.

Preparation calibration curve of Amoxicillin with 0.1 N HCl

The standard solution (100 $\mu\text{g/ mL}$) of pure drug (Amoxicillin) was prepared in freshly prepared 0.1 N hydrochloric acid (pH-1.2). The standard calibration curve of Amoxicillin was obtained by plotting Absorbance V/s. Concentration. Table 1 shows the absorbance

values of amoxicillin. The standard curve is shown in Fig. no.1.

Table:1 Standard Calibration result of Amoxicillin In 0.1 N HCl (pH 1.2)

Sr. No	Concentration (µg/ml)	Absorbance At 310 Nm
1.	3	0.1851
2	6	0.2621
3.	9	0.3590
4.	12	0.4372
5.	15	0.5576
6.	18	0.6841

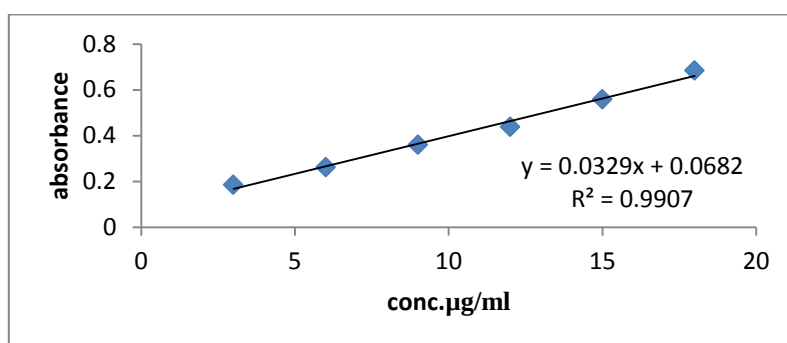


Fig.1 Standard Calibration Curve of Amoxicillin In 0.1 N HCl (pH 1.2)

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose were found between $16^{\circ}.54$ - $21^{\circ}.47$.

Bulk Density

It may be defined as the mass of powder divided by the bulk volume. The bulk density were found between 0.158 -0.278 g/cc.

Tapped Density

It may be defined as the mass of the powder divided by tapped volume. The tapped density were found between 0.225 -0.401 g/cc.

Compressibility Index

It is used to measure the porosity of the powder to be compressed to evaluate the inter particulate interactions. It were found between 27.58 -42.80 which revealed that all powders had excellent to passable flow properties.

Hausner's ratio

It is used to know ease of flow of powder. Hausner's ratio were found between 1.21-1.74 which revealed that all powder blends had good flow properties.

Table :2 Micromeritic Properties of Different Batches of Microspheres

Batch	Angle of Repose (°)	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio
B1	$18^{\circ}.22' \pm 0.22$	0.189 ± 0.002	0.286 ± 0.002	33.62 ± 2.3	1.5112 ± 0.1
B2	$19^{\circ}.06' \pm 0.80$	0.218 ± 0.005	0.374 ± 0.008	38.59 ± 2.7	1.7148 ± 0.08
B3	$20^{\circ}.89' \pm 1.23$	0.228 ± 0.005	0.400 ± 0.016	42.80 ± 1.2	1.7489 ± 0.03
B4	$16^{\circ}.54' \pm 0.99$	0.278 ± 0.004	0.401 ± 0.03	30.07 ± 4.6	1.4341 ± 0.09
B5	$22^{\circ}.05' \pm 1.29$	0.209 ± 0.002	0.326 ± 0.01	35.70 ± 3.1	1.5578 ± 0.07
B6	$17^{\circ}.11' \pm 0.90$	0.274 ± 0.004	0.379 ± 0.008	27.58 ± 0.4	1.3809 ± 0.009
B7	$18^{\circ}.00' \pm 0.5$	0.263 ± 0.007	0.319 ± 0.01	28.55 ± 3.0	1.2140 ± 0.04
B8	$21^{\circ}.47' \pm 0.24$	0.158 ± 0.001	0.225 ± 0.002	30.45 ± 1.4	1.4384 ± 0.02

Percentage yield

The percentage yield of different formulations was determined by weighing the microspheres after drying. The percentage yield was found between 15-36.20%.

Particle size analysis

The particle size analysis was carried out to found the particle size of microspheres. The particle size was found between 585.6-852.7.

Drug entrapment efficiency

Efficiency of drug entrapment was calculated in terms of entrapment efficiency (EE). The drug entrapment efficiency was found between 53.91-89.43.

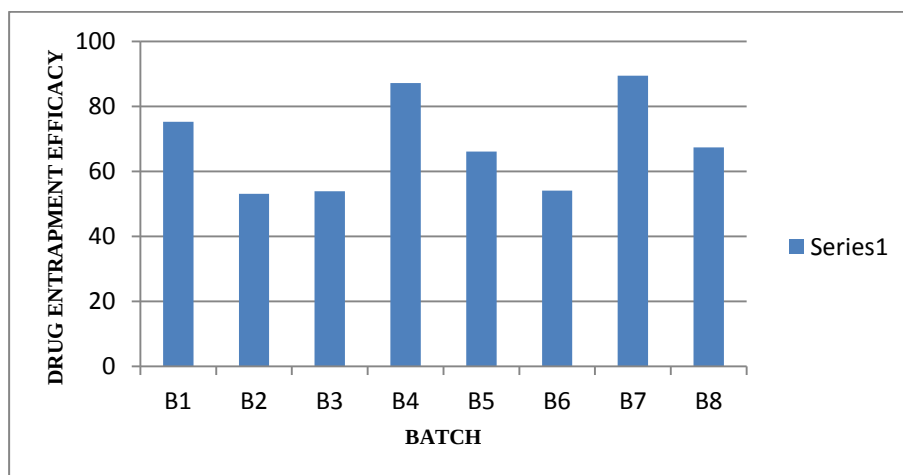


Fig. 2: % Entrapment Efficiency

Mucoadhesive of microspheres

Mucoadhesive properties of the microspheres were evaluated by the *in vitro* wash-off test. It was found between 68.87-91.14.

Swelling study

A known weight of (50 mg) microspheres was placed in a glass vial containing 10 ml of distilled water at $37 \pm 0.5^\circ\text{C}$ in with occasional shaking. It was found between 0.623-1.269.

Table 3: Evaluation Results of all formulations

Sr. No.	Formulation Batch	Percentage Yield (%)	Particle size (μ)	EE (%)	Degree of swelling (a)	In vitro Mucoadhesion (%)
1	B1	30.00	12.8	75.28	0.969	73.16
2	B2	36.20	14.2	53.07	0.7276	75.28
3	B3	16.72	19.5	53.91	0.623	68.86
4	B4	28.50	13.4	89.43	1.36	91.14
5	B5	22.40	12.4	66.13	1.263	81.85
6	B6	50.32	15.6	54.12	1.1428	90.69
7	B7	35.28	18.7	87.18	0.8822	71.32
8	B8	15.00	17.5	67.35	1.2694	89.25

In-Vitro Drug Release Study

Release of amoxicillin from microspheres was evaluated in 0.1 N HCl (pH1.2).

Table 4: In-vitro drug release for all formulations

Sr. No	Time (Hr.)	% drug release							
		B1	B2	B3	B4	B5	B6	B7	B8
1	0	0	0	0	0	0	0	0	0
2	1	21.69±	39.72±	44.75±	17.09±	12.73±	19.38±	16.85±	15.78±
		1.64	0.68	1.37	2.20	0.69	0.39	2.46	0.14
3	2	31.16±	43.69±	51.31±	24.45±	21.02±	25.09±	29.05±	25.35±
		0.14	0.91	3.83	0.55	0.10	0.15	1.36	0.06
4	3	34.90 ±	55.40 ±	59.74 ±	33.80 ±	32.52 ±	32.12 ±	35.17±	31.40±
		1.14	1.86	2.46	2.57	0.79	1.19	0.01	0.09
5	4	40.95 ±	59.19 ±	61.35 ±	46.17±	43.26 ±	40.54 ±	44.34 ±	38.50 ±
		0.12	0.46	2.93	0.38	0.18	0.24	0.55	0.12
6	5	47.16±	64.28±	63.76±	63.48±	62.65±	44.23±	57.39±	46.95±
		0.18	0.52	1.84	1.80	0.18	0.27	0.82	0.11
7	6	51.14	66.98	70.76	78.00	76.14	48.44	75.14	59.76
		± 0.11	± 0.63	± 0.00	± 1.37	± 1.43	± 0.19	± 0.55	± 0.08
8	7	59.82 ±	72.16 ±	75.88±	86.06 ±	85.59 ±	55.61 ±	86.77 ±	67.47 ±
		1.26	2.38	7.28	1.56	2.10	1.39	1.36	0.11
9	8	65.22±	74.72±	77.77±	97.00±	89.68±	67.41±	93.74±	80.21±
		0.09	1.06	6.56	1.29	0.47	0.52	0.96	0.35

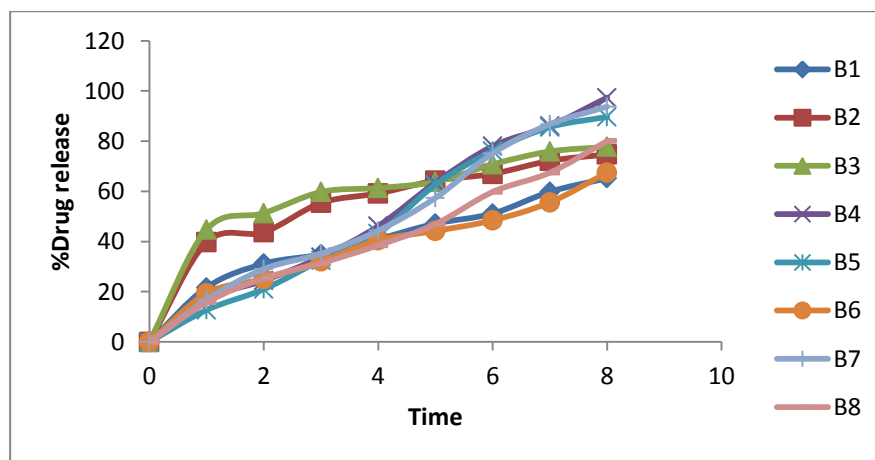


Fig. 3: In-vitro drug release for all formulations

By analysing all the above data, the formulation B4 was found to be the best formulation.

Drug Kinetic

- Drug release kinetics of B4 (best formulation) formulation.

- Drug release kinetics studies for best formulation (B4) were done using software KinetDS3 and it was observed that B4 formulation followed Zero Order, Higuchi, Korsmeyer-peppas, Hixon Crowell drug kinetic model for drug release.

Table 5: Drug kinetic model

Sr. No.	Models	R ² Values
1	Zero Order	0.988
3	Higuchi	0.972

4	Korsemyer – Peppas	0.963
5	Hixon Crowell	0.964

Temperature and humidity studies of best formulation

Table 6: Temperature and humidity studies

Parameters	Days				
	0	7	14	21	28
Appearance	Yellowish White	Yellowish White	Yellowish White	Yellowish White	Yellowish White
Entrapment Efficiency (%)	44.51 ± 0.02	44.51 ± 0.02	43.39 ± 0.04	44.26 ± 0.01	43.63 ± 0.04
Percent Release (%)	92.74 ± 0.3	92.74 ± 0.3	91.89 ± 0.67	91.37 ± 0.73	90.65 ± 0.88

CONCLUSION

Amoxicillin with its comparable clinical efficacy to other antibacterial and favourable dosage, pharmacokinetic profile and tolerability is an excellent candidate to treat various infectious diseases. As it is less effective against gram negative organisms and bacterial resistance

develop to the drug candidate, it is the one area where major development is required. Progression in work is also required to investigate new routes of administration and dosage forms with more efficacies to reduce the dose and associated side effects.

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