INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
ISSN: 2231-6078
3(2): April.-June.: (2013), 629-635

Research Article

Formulation and Evaluation of Amikacin Loaded Microcapsules

Chetan Kanathe *, Shailesh Gupta, Novjoth Singh and Avinash Kundalkar
Department of Pharmaceutics, NRI Institute of Pharmacy, Bhopal, India

Abstract
Amikacin was formulated as a novel sustained release microcapsules using different concentration of the naturally occurring natural polymer ethyl cellulose and HPMC polymer by non solvent evaporation method for sustained release dosage forms. The prepared miocroencapsules of amikacine were evaluated for size analysis, drug content, Swelling Properties, Encapsulation efficiency, percentage of drug release and compatibility. All microcapsules obtained were in desire size, free flowing and spherical in shape. Amikacin release from microencapsule follow non-fickian diffusion and its release profile show zero order kinetics. Amikacin release from the Ethylcellulose, HPMC and both EC+HPMC coated microcapsules was slow and around 12-16 hours release of drug observed
Keywords : Amikacin, ethyl cellulose, HPMC polymer, microencapsules, zero order kinetics.

Introduction
Microenscapsulation has been accepate as a process to achieve controlled release and drug targeting. Sustained release has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form at the site of application or absorption and to facilitate absorption intimate contact of the dosage form with underlying surface to improve the bioavailability of drugs. Several studies has been reported drug delivery system in the form of tablets, films, patches and gels for oral, buccal, nasal, ocular and topical routes.

Microencapsulation is the packaging of small droplets of liquid or particles with a thin film. Typically, the lowest particle size of microcapsules is 1µm and the largest size is 1mm. Microcapsules consist of a core and a wall (or shell). The configuration of the core can be a spherical or irregular particle, liquid-phase suspended solid, solid matrix, dispersed solid and aggregates of solids or liquid forms. The most significant feature of microcapsules is their microscopic size that allows for a huge surface area.

Extremely tiny droplets, or particles of liquid or solid material, are packed within a second material or coated with a continuous film of polymeric material for the purpose of shielding the active ingredient from the surrounding environment. These capsules, which range in size from one micron to seven millimeters, release their contents at a later time by means appropriate to the application.

*** Corresponding Author**
Email : Shailgpharma@gmail.com

The ingredients to be coated are referred to as core, internal phase (IP), encapsulate or fill, whereas terms applied to the coating of the microcapsules include the wall, shell, external phase or membrane. All three states of matter i.e. solid, liquid and gases, may be encapsulated and affect the size and shape of the capsules. If a solid or a crystalline material is used as the core, the resultant capsule may be irregularly shaped. However, if the core material is a liquid, simple spherical capsules, containing a single droplet of encapsulate, may be formed. The capsulated particles produce their required effect when their core material is released. There are four typical mechanisms by which the core material is released from a microcapsule [1-4].

Among different techniques for microencapsulation of functional food ingredients, coacervation (phase separation) is the most common one applied in the food industry. The term coacervation was suggested for the first time by Bungenberg de Jong8 to explain the phenomenon of phase separation in a macromolecular system in which two phases are formed. Simple coacervation refers to phase separation brought about by reducing the solubility of a polymer by changing the temperature, adding non-solvents or “salting-out” by electrolytes, while complex coacervation or “associative” phase separation involves the addition of another oppositely charged macromolecule [5,6]. As a consequence, the system demixes into two phases: a solvent-rich phase containing very small amount of polymer and a polymer-rich phase – coacervate. “Segregative” phase separation occurs due to the thermodynamic incompatibility of two polymers, which results in system demixing into two phases, each phase rich with one of the two polymers.In microencapsulation processes by coacervation method, the material to be encapsulated is emulsified or dispersed in a solution of a polymer, and by changing the temperature, pH value or adding another polymer or non-solvent, coacervation can be induced, where the coacervate deposits at the surfaces of the dispersed particles and forms a thin coating. After further treatment, in order to solidify the polymeric wall, microcapsules can be obtained and separated from the system. The coacervation method of microencapsulation was recently adopted for coating nanoparticles for electronic paper application. The most commonly used wall materials in microencapsulation by coacervation processes are proteins, gums, carbohydrates and various synthetic polymers [7,8]

Amikacin is a semi-synthetic aminoglycoside antibiotic derived from kanamycin A. Amikacin is most often used

usually by reducing the dosing frequency. for treating severe, hospital-acquired infections with multidrug resistant Gramnegative bacteriasuchas Pseudomonasaeru ginosa, Acinetobacter and Enterobacter. Serratia marcescens and Providencia stuartii are also included in the spectrum. Amikacin can also be used to treat non tubercular mycobacterial infections and tuberculosis (if caused by sensitive strains) when first line drugs fail to control the infection. Amikacin may be combined witha beta-lactam antibiotic for empiric therapy for people with neutropenia and fever.

The drug amikacin has been selected as suitable candidate for site specific delivery by encapsulating it in microcapsules. Due to reasons dose of conventional tablet 500mg (2 times a day), it is a typical task to administered tablet 2 times in a day, but must be given by the intravenous, via nebulization, or intramuscular route. In people with kidney failure, dosage must be adjusted according to the creatinine clearance,

Materials and Methods

Materials :

Amikacin was a kind gift sample to Zee laboratory, Konta, Himachal Pradesh. Methanol was purchased from Ranchem Lab, Delhi. All other chemicals used in our work were of analytical grade.

Preparation of Microcapsules :

Amikacin microcapsules were prepared by Emulsion Solvent Evaporation method The polymer (2g) was dissolved in 18 ml of acetone. Amikacin (500 mg) was added to the polymer solution (18 ml) and mixed thoroughly. The resulting mixture was added in continuous phase made up of ethanol (2ml) and magnesium stearate (50mg) in a 500 ml beaker while overhead stirring at 600 rpm to emulsify added droplets. Stirring was done for 15 min in magnetic stirrer and then continued further with mechanical stirrer to evaporate the solvent for 3 hr. Microcapsules were obtained by decantation and washing with cyclohaxane. The product was then dried at room temperture for 24 hr to obtain discrete microcapsules [9].

Evaluation of Microcapsules :

Percentage (%) yield:

The yield of microsphere was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug.

$$\text{Percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total Weight of drug and polymer used}} * 100$$

Particle size analysis:

For size distribution analysis, different sizes in a batch were separated by sieving; using a set of standard sieves (IP) [10]. The amounts retained on different sieves were weighed.

Encapsulation efficiency:

Drug loaded microcapsule (10 mg) were powdered and suspended in 10 m 0.1 n HCL solutions and kept for 24 hrs. It was stirred for 5 min and filtered by whatman filter paper. For determination of entrapped drug, the amount of drug present in the clear supernatant after centrifugation was determined by UV spectrophotometer at 360 nm. A standard calibration curve is plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation. Effectively will give the amount of drug added entrapped in the particles. [10,11]

The drug entrapment efficiency was calculated by the following equation

$$\% \text{ Entrapment Efficiency} = \frac{Pc}{Tc} * 100$$

Where, Pc = Practical content

Tc = Theoretical content

Estimation of Drug Content:

Amikacin drug content in the microcapsules was calculated by UV spectrophotometric (Systronic 1200) method. The method was validated for linearity, accuracy and precision. A sample of microcapsules equivalent to 100 mg was dissolved in 25 ml ethanol and the volume was adjusted upto 100 ml using phosphate buffer of pH 6.8. The solution was filtered through Whatman No. 1 filter paper. Then the filtrate was assayed for drug content by measuring the absorbance at 360 nm 13 after suitable dilution [11,12].

Wall thickness:

Wall thickness of amikacin microcapsules was determined by the method of using equation.

$h = r (1-p) d1 / 3[pd2 + (1-p) d1]$

where as:

h = wall thickness of microcapsules

r = arithmetic mean radius

d1 = density of core material

d2 = density of coat material

p = proportion of medicament in microcapsules

Determination of swelling properties:

The dynamic swelling property of microcapsules in the dissolution medium was determined. Microcapsules of known weight were placed in dissolution solution for 4 hrs. and the swollen microcapsules were collected by a centrifuge and the wet weight of swollen microcapsule was determined by first blotting the particles with filter paper to remove absorbed water on surface and then weighing immediately on a electric balance. The percentage of swelling microcapsules in the dissolution media was then calculated by using equation. [10,13]

$$Sw = \frac{(Wt - Wo)}{Wo} \times 100$$

Where Sw = percentage of swelling of microcapsules
Wt = weight of microcapsule as time t
Wo = initial weight of microcapsule

Determination of Rheology Properties:

Angle of repose, cars, index, bulk density, and hausner ratio were determined to assess the flow ability of the prepared microcapsules.

Determination of percentage of moisture loss:

The amikacin loaded microcapsules was evaluated for percentage of moisture loss which sharing an idea about its hydrophilic nature. The microcapsules weighed initially kept in desiccators containing calcium chloride at 37 c for 24 hours. The final weight was noted when no further changes in weight.

$$\% \text{ Moisture loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} * 100$$

In-Vitro Release Studies:

In vitro dissolution studies were performed using USP type I dissolution apparatus at 75 rpm. The micro capsules were weighed and filled in the empty capsule shells and placed in the basket.buffer pH 7.4 used for dissolution study from 3rd to 12th hour, Temperature was maintained at 37°C ± 5°C. An aliquot (5 mL) was withdrawn at specific time intervals and rephenished with an equivalent volume of dissolution fluid. The aliquot sample was dissolve in reagent for derivatization process. The derivaatization sample was analysed by UV - visible spectrophotometer at 360 nm. The release studies were conducted in triplicate Experimental results were expressed as mean ± SD. Student's t-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at $p < 0.05$. The statistical software used for analysis was GraphPad Prism Software Version 4.0 (GraphPad Prism Software, San Diego, CA, USA). [14-18].

Results and Discussion

FTIR studies shows that there is no interaction between the drug and the polymer used. This was shown in figure no 9.1, 9.2. Various polymer ratios were used to formulate the microcapsules and these formulations are shown in table no 9.6 the Scanning electron microscopy revels that size of prepared microcapsules and was shown in fig no 9.3. The yield of the microcapsules were high for F-3 comparing to other 2 formulations and encapsulation efficiencies were high for all the formulations and were not affected by the type of polymer and drug polymer ratios and strring speed. The in-vitro release of the drug from microcapsules were studied by pH 7.4 phosphate buffer using type II basket method. The results are given from this study, it shows that the release ratios were very slow in as we go on increasing the polymer ratio the release of the drug is sustained. Among all the formulations the drug release was more.

Conclusions:

Microcapsules of amikacin could be prepared by the solvent evaporation method developed. The result of the present study demonstrated that the prepared microcapsules from the Ethylcellulose, HPMC and both EC+HPMC coated were sustained the release from 12-16 hours. This can be reduced the frequency the dose administration of amikacin tablet and reduced the dose dependant side effect of the amikacin tablet.

Acknowledgements

Authors are thankful to Zee Laboratory konta H.P., India for the gift samples of amikacin drug and we are very thankful to Dr. Avinash Kondalkar, Principle of NRI Institute of Pharmacy Bhopal,M.P.,India for kind help and providing laboratory facilities to carry out the project work.

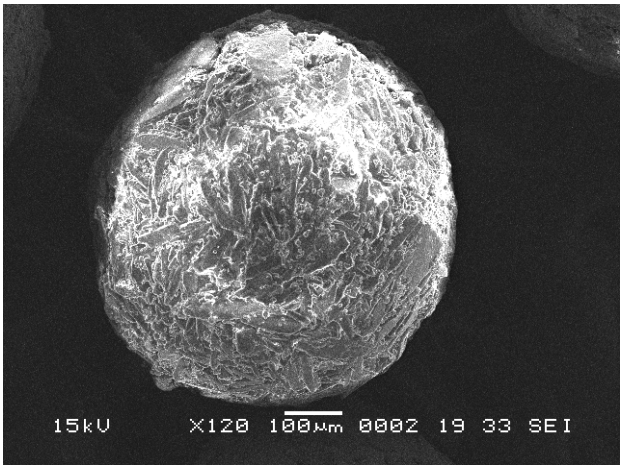


Fig 3: SEM image of Amikacin microcapsule using EC & HPMC

Table 1: Percentage Yield, Drug Content of Amikacin loaded microcapsule

Formulation	Yield (%)	Theoretical drug content (mg)	Practical Content (mg)	Encapsulation efficiency (%)
F1	73.33	30	22	51.69
F2	78	30	23.4	54.84
F3	82.66	30	24.8	64.53

Table 2: Partition Coefficient Values of Drug

Sr. No.	Medium	Partition Coefficient (Log P)
1	n – octanol : Water	2.94
2	Cyclohexane : Water	20.6

Table 3: Percentage Yield, Drug Content of Amikacin loaded microcapsule

Formulation	Yield (%)	Theoretical drug content (mg)	Practical Content (mg)	Encapsulation efficiency (%)
F1	73.33	30	22	51.69
F2	78	30	23.4	54.84
F3	82.66	30	24.8	64.53

Table 4: Swelling Properties of Amikacin microcapsule

Formulation	Initial Weight (mg)	Final Weight (mg)	% Swelling
F1	50	89	78
F2	50	91	82
F3	50	99	98

Table 5: Various Rheology Properties of Amikacin Microcapsule

Formulation	Carr's Index	Hausner Ratio	Angle of repose
F1	12.5	1.14	20.7
F2	9.82	1.09	23.6
F3	8.0	1.08	26.5

Table 6: Moisture loss of Amikacin microcapsule

Formulation	Initial Weight (mg)	Final Weight (mg)	Moisture Loss	% Moisture Loss
F1	200	191.25	8.75	4.57
F2	200	189.25	10.75	5.68
F3	200	187.25	12.75	6.80

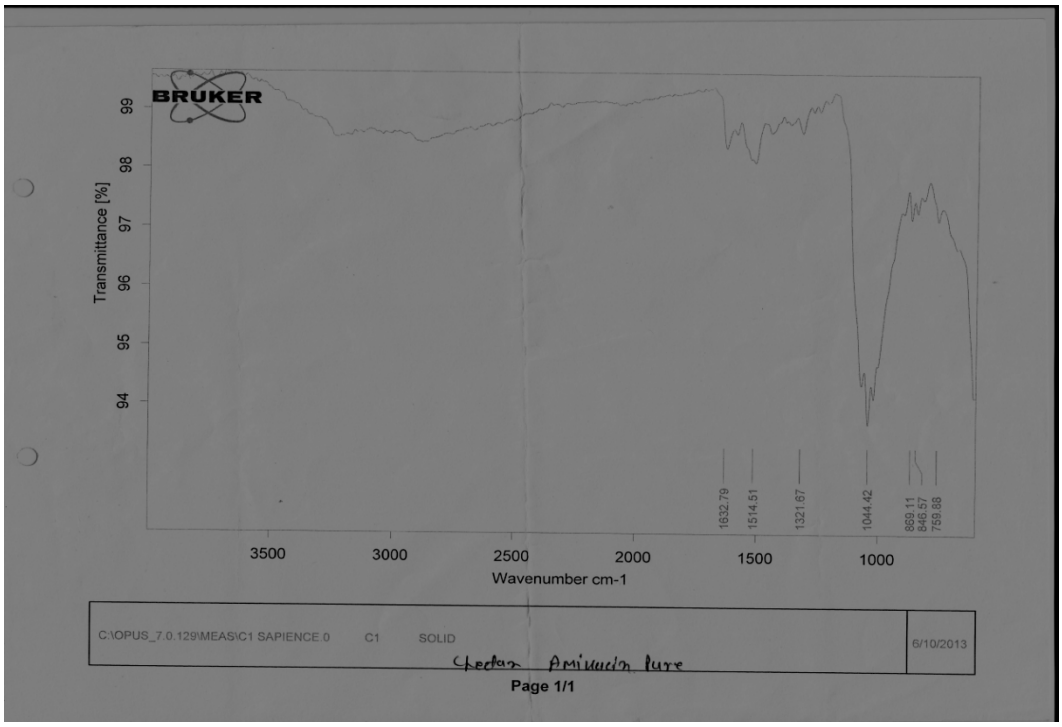
Table 7: Drug Release Study of Amikacin microcapsule using EC+HPMC

S.No	Time (hr)	Cumulative % of Drug Release
1	1	12.128
2	2	16.75
3	4	24.841
4	6	33.587
5	8	44.659
6	10	53.671
7	12	57.631
8	16	68.981
9	20	79.231
10	24	85.561

Table 8: Correlation coefficient (R^2) and constant (K) of different kinetic models for Amikacin Microcapsules

Microcapsules	Zero Order		First Order		Higuchi Equation		Pappas Equation	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_P
HPMC	**0.985**	**3.797**	**0.963**	**19.75**	**0.976**	**0.598**	**0.976**	**0.598**
EC	**0.973**	**3.737**	**0.982**	**20.96**	**0.977**	**0.575**	**0.977**	**0.575**
HPMC+EC	**0.958**	**3.489**	**0.984**	**18.6**	**0.992**	**0.649**	**0.992**	**0.649**

Fig 1. FTIR of Amikacin



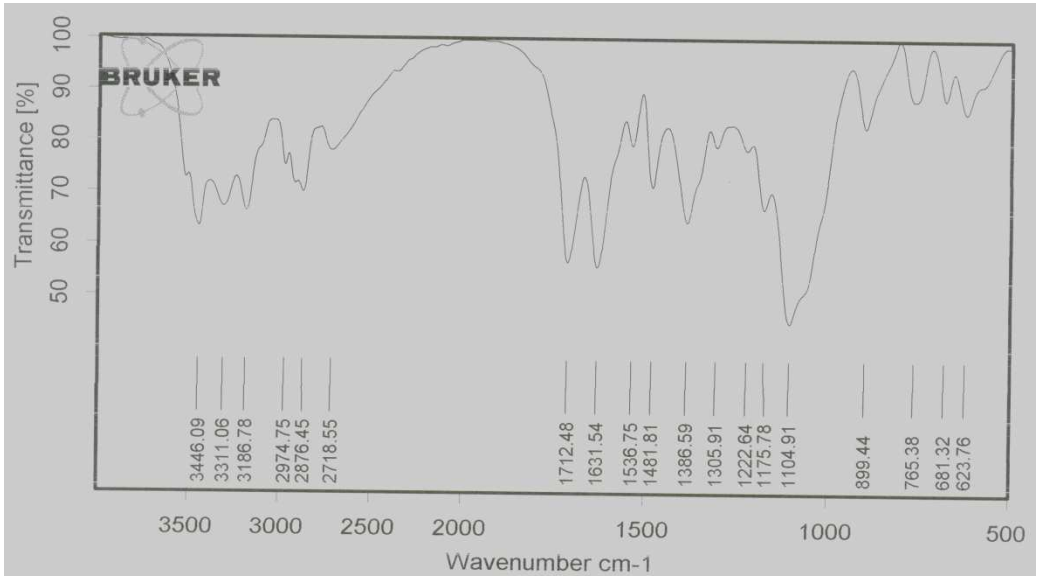
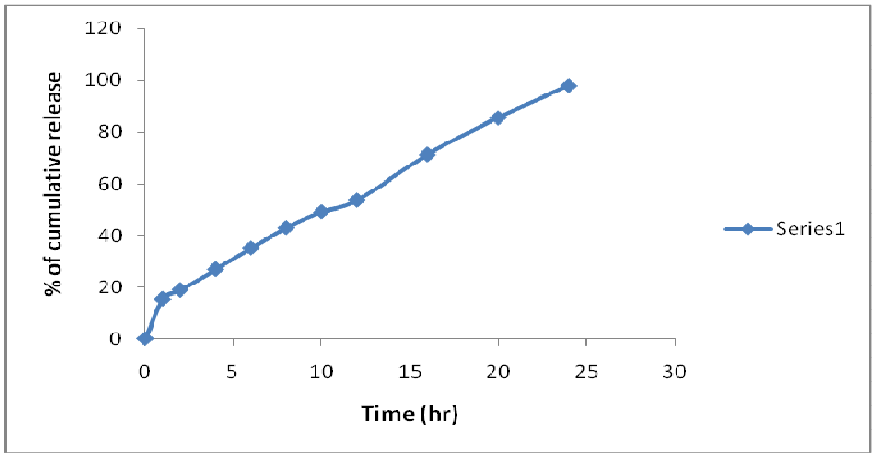


Fig 2. FTIR of Amikacin + Ethyl Cellulose+HPMC



Graph 4 : Release Pattern of Amikacin Microcapsule using EC and HPMC

References :

1) K.Shekhar, M.Naga Madhu, B.Pradeep, David Banji Review on micro encapsulation Department of Pharmaceutics, Nalanda College of Pharmacy, Nalgonda. ,2010 ,5: 58.
2) Alagusundaram M, Chetty MS, Umashankari C. Microspheres as a Novel drug delivery system – A review. Int J Chem. Tech. 2009;12:526-34.
3) Banker G S, Rhodes C T. Modern pharmaceutics. In Parma Publication, 2002, 121: 501-527.
4) C. Thies, in Microencapsulation: Methods and industrial applications, S. Benita, Ed. Marcel Dekker, New York, Basel, 1996, 1.
5) C. Thies, in Microencapsulation: Methods and industrial applications, S. Benita, Ed. Marcel Dekker, New York, Basel, 1996, 1.
6) H. S. Kas, L. Oner, in Handbook of pharmaceutical controlled release technology, D. L. Wies, Ed., CRC Press, London, 2000, 301.
7) A. Gharsallaoui, G. Roudaut, O. Chambin, A. Voilley, R. Saurel, Food Res. Int. 40 (2007) 1107.
8) S. Gouin, Trends Food Sci. Technol. 15 (2004) 330.
9) Yadav A.V, Shete A. S, Dabke A.P and Shinde V.R., Formulation and In-vitro Evaluation of Aceclofenac Microcapsules, International Journal of PharmTech Research, 2009; 1(2): 135-138.
10) Indian Pharmacopoeia, 3rd ed. Delhi: Controller of publications, 1996, vol.-II, A-7
11) Dua K., Ramana M.V., Sara U.V.S., Himaja M., Garg V., Agarwal A., Dissolution enhancement of aceclofenac through solid dispersion, Indian Pharmacist., 2006,48,70-72.
12) Chowdary K.P.R. and Koteshwara R., Ethyl cellulose microsphere of Glipizide: Characterization in vitro and in vivo evaluation, Indian J. pharm. sci., 2004, 66, 4, 412-416.
13) Madziva H, Kailasapathy K, Phillips M. Alginate-pectin microcapsules as a potential for folic acid delivery in foods. J Microencapsul. 2005;22:343–51.
14) 66. Bakan JA, Swarbrick J, Boylan J. Encyclopedia of pharmaceutical technology, vol. 9. New York: M. Dekker; 1994. p. 423–41.
15) 67. Suzuki K, Price JC. Microencapsulation and dissolution properties of a neuroleptic in a biodegradable poly (d, 1-Lactide). J Pharm Sci. 1985;74:21–4.
16) 68. Rafienia M, Orang F, Emami SH. Preparation and characterization of polyurethane microspheres containing theophylline. J Bioact Compat Polym. 2006;21:341–9.
17) 69. Zhang WF, Chen G, Li PW, He QZ, Zhou HY. Chitosan and chitosan/β-cyclodextrin microspheres as sustained-release drug carriers. J Appl Polym Sci. 2006;103:1183–90.
18) 70. Sanchez LC, Teresa FM, Fernandez AM, Alvarez FJ, Rabasco AM, Mura P. Development of sustained release matrix tablets of didanosine containing methacrylic and ethylcellulose polymers. Int J Pharm. 2002;234:213–21.