Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

# Modification of Ciprofloxacin HCl release from Povidone K-30 based Matrix as a Function of Avicel pH 101

JAKIA SULTANA[1], MOHAMMAD SALIM HOSSAIN[1], MUHAMMAD SHAHDAAT BIN SAYEED[2], S.M. ASHRAFUL ISLAM[3] MOHAMMAD SAFIQUL ISLAM[1*]

[1]Department of Pharmacy, Noakhali Science and Technology University, Sonapur, Noakhali-3802, BANGLADESH
[2]Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, BANGLADESH
[3]Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, BANGLADESH

**ARTICLE DETAILS**

*Article history:*
Received on 10 February 2012
Modified on 15 April 2012
Accepted on 20 April 2012

*Keywords:*
Matrix tablets,
Ciprofloxacin HCl,
Povidone K-30,
Avicel pH101

**ABSTRACT**

Controlled release matrix tablets of Ciprofloxacin HCl were prepared and evaluated as the function of varying the concentrations of polymers e.g., Povidone K-30and excepients e.g, Avicel pH 101. The concentrations were varied to investigate whether these variations can cause any change in release of Ciprofloxacin HCl molecule. Tablets were prepared by direct compression method .The granules were evaluated for drug content and drug excipient interaction. The tablets were subjected to thickness, diameter, hardness and *in vitro* release studies. The USP Basket method was selected to perform the dissolution test carried out in 1000 ml 0.1 N HCl for 8 hours with 50 rpm , at 37±0.5$^0$C.The release rate was quantitatively determined by a UV-spectrophotometeric method. By comparing the dissolution profiles, it is revealed that significant differences were found among the drug release profile from different formulations matrices. From the study it is found that, Povidone K-30 based matrix tablets release greater percentage of active drug with incorporating the increasing amount of Avicel pH101. The release of active drug from the prepared matrix tablet appears to follow the Higuchi kinetics model. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism was diffusion controlled or Fickian transport which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion in all cases.



## INTRODUCTION

Long term treating of any disease requiring high frequency administration of drug is a cumbersome practice for any patient. To avoid such problems sustain release dosage form are much better alternative compared to conventional dosage form because administration of one single sustain release dose maintain the desired drug plasma level [1].The release of drug from particle depend on the polymer used to form particle and the quantity of drug contained in it. In the last two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance [2].

***Author for Correspondence:***
*Email:* research_safiq@yahoo.com

Sustained release tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substances (various: some acrylates, even chitin, these are often patented) so that the dissolving drug has to find its way out through the holes in the matrix. In some SR formulations, the matrix physiologically swells up to form a gel, so that the drug has first to dissolve in matrix, and then exit through the outer surface [3]. Extensive In-vitro and In-vivo studies of such dosage form are done to make it more and more safe and effective toward treatment of diseases [2].

Ciprofloxacin is a broad spectrum antibiotic and its half-life in plasma has been reported to be 4 to 5 hours [4]. The shorter biological half-life and frequent dosing in wide varieties of bacterial and protozoa infections make it as an ideal candidate for sustained drug delivery system. Therefore the objective of the work is to provide a sustained action pharmaceutical composition

containing Ciprofloxacin HCl in a modified release formulation, to maintain the blood levels of the active ingredient for a prolonged period of time.

In the present study, we aimed to study the effect of some release modifiers on the release of Ciprofloxacin (CIP) HCl from the matrix tablets using different mathematical models (Zero order, First order, Higuchi's model, Korsmeyer-Peppas model) to investigate the release kinetics of Ciprofloxacin HCl in conjunction with varying amounts of excipients.

## MATERIALS AND METHODS

Ciprofloxacin HCl was donated by Drug International Ltd. Povidone K-30(polyvinyl pyrrolidone K-30) and Avicel pH 101were procured from Loba Chem. Pvt. Ltd, India. Magnesium stearate was obtained from Hanau Chemicals Limited, Japan. Various methods are available for producing controlled release ciprofloxacin preparation. In our experiment direct compression technique was followed to prepare sustained release Ciprofloxacin matrix tablet.

### Preparation of Granules for Matrix Tablets

The required amount of active drug and excipients were accurately weighed and mixed thoroughly. Then magnesium stearate was added and the prepared granules were then subjected to compression. Table 1 represents the formulation of matrix tablets with their formulation code.

### Preparation of Matrix tablets by Direct Compression Technique

The method includes blending of the active ingredients with filler, lubricant and flow promoter followed by direct compression. The amount of active drug was constant (750mg) in all cases. Total weight of tablets was 1003 mg. Matrix tablets were prepared by Hydraulic Press fitted with a diameter 13 mm punch applying a compression force of 4 ton. All the tablets were then stored in air tight containers at room temperature for further investigation.

### Dissolution studies

At first, the medium of the dissolution-0.1 N HCl was prepared by taking 8.36 ml of 37% conc. HCl in 1000 ml volumetric flask. 900 ml water was added to dissolve and finally water was added q.s. to 1000 ml. The dissolution parameters were set, where the rpm was 50, temp was $37^0$C in the dissolution test apparatus II (Rotating paddle method). A single tablet was placed (for every formulation 2 tablets in different 2 beakers) in a dissolution medium contained 0.1 N HCl solution (900 ml) and was started the dissolution machine. The solution from the medium after 15, 30, 45 minute and 1, 1.3, 2, 3, 4, 5, 6, 7, 8 hour was withdrawn. The volume of withdrawn solution was 5 ml respectively to times. After withdrawing, the same volume (5 ml) of 0.1 N HCl solutions was added in dissolution medium at the time schedule. The absorbance was measured with the help of UV-spectrophotometer at the wavelength of 276 nm. The absorbance value was put in straight line equation and found the concentration of drug in 900 ml dissolution medium and also found the cumulative drug release (CDR).

Then the percentage of drug release was calculated by using following equation;

% of Drug Release=
CDR (Cumulative drug release)/750×100

### Kinetic Modeling of Drug Release

After completing in vitro dissolution of all the batches for eight hours, the release data were fitted to the following equations to analyze the mechanism of drug release from the matrix tablets,

[5]Zero order equation: $Q=K_0t$ …….. (1)

Where Q is the amount of drug release at time t and $k_0$ is the release rate constant;

First-order equation: $Q=K_1C$ ……..(2)

Where the percent of drug release at time t and $K_1$ is the release rate constant;

[6]Higuchi equation: $Q=K_Ht^{1/2}$ ……..(3)

Where Q is the percent of drug release at time t and $K_H$ is the diffusion rate constant

The Zero order and Higuchi models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer kinetic equation [7] to ascertain the mechanism of drug release.

$\log (Qt/Q\infty) = \log K + n \log t$ …….. (4)

Where,$Q\infty$ is the amount of drug release after infinite time; K is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusion exponent or release exponent; indicating the mechanism of drug release.

**Table 1:** Formulations of Ciprofloxacin HCl loaded Matrix Tablets Prepared by Direct Compression Method

| Ingredients(mg) | Amount in mg(each tablet) Formulation Code | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Ciprofloxacin HCl | 750 | 750 | 750 | 750 |
| Povidone K-30 | - | 150 | 200 | 250 |
| Avicel pH 101 | 250 | 100 | 50 | - |
| Mg-stearate | 3 | 3 | 3 | 3 |

**Table 2:** Physical Parameters of Ciprofloxacin HCl loaded Matrix Tablets of Different Formulations

| Formulation code | Weight variation (mg) | Hardness (kgf) | Thickness (mm) | Diameter (mm) | Drug content (mg) | % of content |
|---|---|---|---|---|---|---|
| F-1 | 1004.38±0.968 | 47.18±0.634 | 6.01±0.0045 | 13.00±0.0234 | 744.58 | 99.43% |
| F-2 | 1004.57±1.127 | 46.46±0.725 | 6.01±0.0040 | 13.01±0.0277 | 753.98 | 100.57% |
| F-3 | 1003.54±1.453 | 45.60±0.262 | 6.00±0.0026 | 13.00±0.0258 | 732.88 | 97.67% |
| F-4 | 1004.01±1.141 | 45.65±0.175 | 6.01±0.0025 | 13.00±0.0277 | 740.1 | 98.42% |

For a tablet having cylindrical shape, when n is below 0.5, the Fickian diffusion phenomenon dominates, and n between 0.5 and 1.0 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 1.0 the release can be characterized by case II and above 1.0 the release can be characterized as super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer [8-9].

## RESULTS AND DISCUSSION

### Drug content and Physical evaluation of Ciprofloxacin HCl matrix tablets

The tablets of different formulations were subjected to various evaluation tests, such as weight variation, hardness, thickness and diameter according to procedure specified in British Pharmacopoeia. The granules were tested for drug content and drug excepients compatibility. The physicochemical compatibilities with the excipients used were tested by measuring the UV-spectra of Ciprofloxacin HCl and Formulated tablets. The UV-spectrophotometer results showed Ciprofloxacin HCl was compatible with excepients.

Weight variation, hardness, thickness and diameter that are carried out in these experiments are presented in Table-2.The weight variation was less than 2%. It is well established that the hardness of the tablet could markedly affect the release rate of drug [10]. Usually, an increase in hardness of a tablet is accompanied by a decrease in release rate, due to a porosity of the tablet [11]. As there is no significant change in the hardness of matrix tablet with change in the hardness of sustained release polymer, the release rate of Ciprofloxacin HCl from matrix tablets is not influenced by the tablet hardness.

From the result obtained from the Table-2, it is found that there is a very minor deviation in case of both diameter and thickness. Though all the formulations were prepared by using the same dies and punch and the pressure applied was around 4 ton, there is no change in thickness and diameter with the increase in concentration of Povidone K-30 and Avicel pH101. Good uniformity in drug content was found among different formulation of tablets, and the percentage of drug content was more than 97%.
All the tablet formulations showed acceptable pharmaco-technical properties and complied with in-house specifications for weight variation, hardness, thickness and diameter.

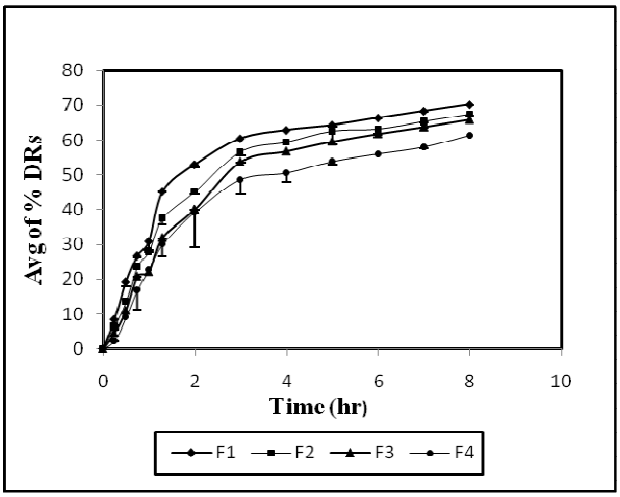


**Figure1:** Zero Order Plot of Release Kinetics of Ciprofloxacin HCl Matrix Tablets.

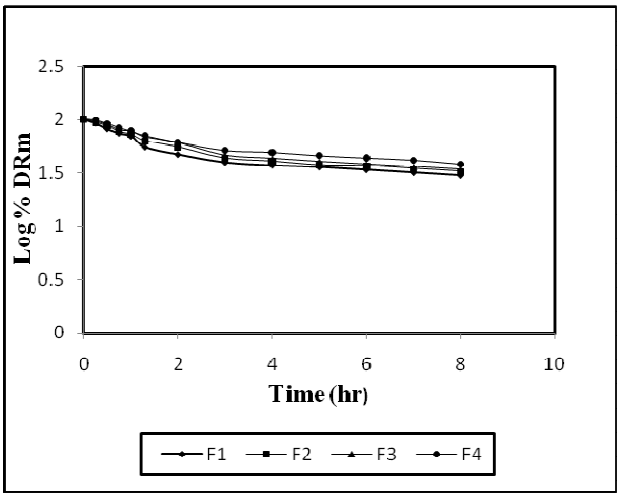


**Figure2:** First Order Plot of Release Kinetics of Ciprofloxacin HCl Matrix Tablets

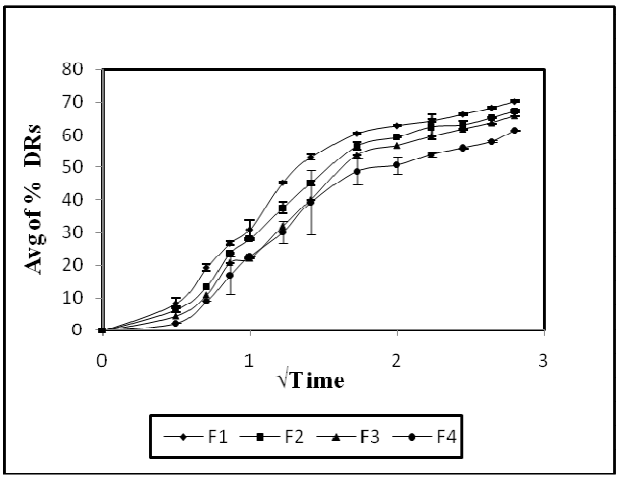


**Figure 3:** Higuchi Plot of Release kinetics of Ciprofloxacin HCl Matrix Tablets

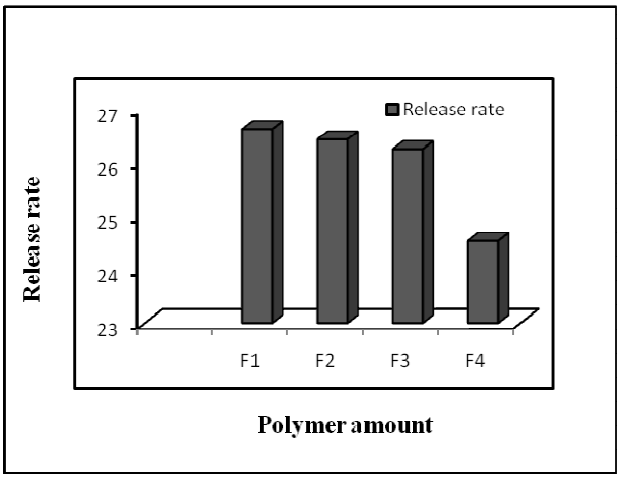


**Figure 4:** Bar Diagram showing Effect of Avicel pH101 and Povidone K-30 concentrations on Release rate (Higuchi release).

**Table 3:** Kinetic Parameters of Ciprofloxacin HCl release from different Polymeric Matrix Tablets

| Formulation code | Zero order plot | | First order plot | | Higuchi plot | | Hixson-Crowell Plot | | Korsmeyer-Peppas plot | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | $K_{H-C}$ | $R^2$ | n |
| F1 | 0.752 | 7.730 | 0.852 | -0.062 | 0.921 | 26.62 | 0.475 | 0.294 | 0.888 | 0.548 |
| F2 | 0.799 | 7.816 | 0.880 | -0.060 | 0.943 | 26.43 | 0.523 | 0.308 | 0.891 | 0.657 |
| F3 | 0.838 | 8.030 | 0.907 | -0.059 | 0.955 | 26.25 | 0.570 | 0.324 | 0.914 | 0.707 |
| F4 | 0.832 | 7.372 | 0.900 | -0.051 | 0.950 | 24.53 | 0.572 | 0.325 | 0.864 | 0.807 |

**Effects of Avicel pH 101 and Povidone K-30 on release pattern of Ciprofloxacin HCl matrix tablets**

After preparing the matrix tablets according to the formulation shown in Table-1, the drug release kinetics from the matrix tablets was studied by using 0.1 N HCl at $37^0$C temperature and 50 rpm paddle speed of a pharma test dissolution apparatus. Samples were collected for 8 hours and percentage of drug release at different time interval was calculated from the UV absorbance reading and 0.1 N HCl was used as the dissolution medium. To determine the effects of Avicel pH101 and Povidone K-30 on drug release, the data was treated with different kinetic models such as, zero order, first order, higuchi, korsmeyer-peppas equations.

The percent release of ciprofloxacin was plotted against time to get zero order plots. Again the log percent remaining was plotted against time to get first order plot. In addition the percent release of ciprofloxacin was plotted against square root of time to get the Higuchi plot.

Four formulations were prepared to investigate the effects of Avicel pH101 and Povidone K-30 and their content level on drug release. Formulation F1, F2, F3 and F4 having a highest regression coefficient ($R^2$:0.921, 0.0.943, 0.955 and 0.950 respectively) (Table-3) towards Higuchi's model, indicating Fickian diffusion through porous matrix. Diffusion is related to transport of drug from the dosage matrix. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics [1].

To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation[2]. The formulations showed good linearity ($R^2$:0.888, 0.891, 0.914, 0.864), indicating that diffusion was the predominant mechanism of drug release from these formulations. The values of release exponent (n) for the above formulations are 0.548, 0.657, 0.707 and 0.807 respectively which indicates anomalous transport mechanism (coupling of the diffusion and erosion mechanism)[13].

The drug release also fitted into first order kinetic model to high extent. It indicates the drug release is dependent on the concentration of Ciprofloxacin hydrochloride.

The effect of polymer content on drug-release as a function of time was found to be significantly different for a specific set of drug and polymer irrespective of their chemical nature [14]. The effect of different concentration of Avicel pH 101 on drug release characteristics of Ciprofloxacin HCl with 50,100 and 250 mg of Avicel pH 101 and the average drug released was 65.93, 67.32 and 70.31 percent after 8 hours are elaborates in Fig. 1-3. Avicel pH 101 caused extensive amount of drug to be released in to the dissolution media. Generally incorporation of Avicel pH 101 result in an increase in the drug release rate due to an increment in total porosity of the matrices ( initial porosity plus porosity due to the dissolution of the drug) [15].

The time required to release 25, 50 and 75 percent of CIP HCl from Formulation F1, F2, F3 and F4 was calculated form Higuchi equation and presented in the following Table 4.

**Table 4:** The Values of t25%, t50% and t75%of Formulated Tablets

| % of release | Time (hr) Formulation code | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| $t_{25}$%(min) | 0.61 | 0.84 | 1.08 | 1.25 |
| $t_{50\%}$( min) | 2.95 | 3.46 | 4.00 | 4.58 |
| $t_{75\%}$( min) | 7.07 | 7.87 | 8.66 | 9.97 |

In case of Povidone loaded matrix tablet, F4 containing highest amount and the drug release was 61.35 percent. The release rate of Ciprofloxacin HCl from Povidone K-30 was least. Rate of drug release tend to decrease with an increase in the content of Povidone K-30. This is in an agreement with the literature [16,17] finding that the viscosity of gel layer around the tablet increases with increase in the hydrogel concentration, thus limiting the release of the active ingredient. It leached slowly from the matrix, for that it slower the release rate. Moreover, Ciprofloxacin (CIP) is highly water soluble drug with pKa value 6.09 & 8.62 [18]. Among four formulations, release rate was increased with increasing the amounts of Avicel pH101 and decreasing amounts of Povidone K-30. A bar diagram was prepared in which the release rate was calculated from the slope of the Higuchi equation showing the effects of Avicel pH101 and Povidone K-30 (Fig. 4).

## CONCLUSION

Subsequent release profiles were performed to evaluate the performance of Ciprofloxacin HCl when formulated with varying concentrations of povidone K-30. Variation in the amount of polymer present significantly affected drug release from prepared matrix tablets. From this study, it can be stated that, Povidone K-30 and Avicel pH 101 based formulations showed significant difference in release pattern. Povidone K-30 containing formulation released lowest amount of drug and Avicel pH 101 containing matrix system released about 70% of drug. While fitting the release kinetics in model dependent approaches, most of the release patterns were fitted to Higuchi's model with Fickian diffusion release mechanism. The release

was dependent on drug diffusion and polymer relaxation. From the results of the present study it appears that the release of Ciprofloxacin HCl was significantly influenced by the characteristics of the polymer and excipient used.

**ACKNOWLEDGEMENT**

The authors are thankful to Globe Pharmaceuticals Ltd. for their generous donation of Ciprofloxacin HCl. The authors are also thankful to all the teachers and staffs of The University of the Asia Pacific for their support and cooperation.

**REFERENCES**

[1] Chib R, Sanker M, Hooda A. Design, formulation and evaluation of sustain release dosage form, Drug Invention Today, 2010;2(8):397-399.

[2] Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems, Journal of Controlled Release, 2002;79(1): 7-27.

[3] Chien YW. Novel Drug Delivery System, 2nd ed. New York: Marcel Dekker, 1992.

[4] Chasin M, Langer R. Responsive Polymeric Delivery Systems, Adv Drug delivery Systems, New York: Marcel Dekker, 1990.

[5] Mockel JE, Lippold BC. Zero order release from hydrocolloid matrics. Pharm.Res, 1993; 10:1066-1070.

[6] Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J.Pharm.Sci. 1961; 50:874-875.

[7] Korsmeyer RW, Gurny R, Doelkar E, Buri P and Peppas NA.Mechanism of Solute Release form Porous Hydrophilic Polymers Int. J.Pharm. 1983; 15:25-35.

[8] Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Int.J.Pharm. 1985; 15:25-35.

[9] Chueh HR, Zia H, Phodes CT. Optimization of Sotalol floating and bioadhesive extended release tablet formulations. Drug Dev.Ind.Pharm. 1995; 21:1725-1747.

[10] Pather I, Russell I, Syce JA, Neau SH. Sustained release Theophyline tablets by direct compression, Part 1: formulation and in vitro testing. Int. J. Pharm.1998; 164: 1-10.

[11] Jovanovic M, Jokic D, Duric Z, Tasic L, Jovicic G. Preparation and preliminary evaluation of sustained-release acetylsalicylic acid tablets. Pharmazi. 1990; 45: 869.

[12] Raymond CR, Paul JS, Owen SC. Handbook of Pharmaceutical Excepients, 5th ed. Pharmaceutical Press and American Pharmacists Association, London, 2006,132-134,430-433,611-616.

[13] Capan Y. Influence of technological factor on formulation of sustained release tablets, Drug Dev. Ind. Pharm. 1965; 15: 927-956.

[14] Katikaneni PR, Upadarshta SM, Neau SH, Mitra AK.Ethyl cellulose matrix controlled release Tablets of a Water soluble drug. Int. J. Pharm. 1995; 123: 119-125.

[15] Fassihi RA, Ritschel. Multiple Layer, Direct Compression Controlled Release System: *In vitro* and *in vivo* Evaluation. J. Pharm.Sci.W.A. 1993; 52:750-754.

[16] Vazques MJ, Perez-Marcos B, Gomez-Amoza JL, Martinez-Pacheco R, Souto C, Concheiro A. Influence of technological variables on release of drugs from hydrophilic matrices. Drug Dev Ind Pharm.1992; 18:1355-1375.

[17] Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methyl cellulose matrices. Int J Pharm. 1985; 24:327-338.

[18] Theeuwes F. Elementary osmotic pump. J Pharm Sci. 1975;64(12):1987-91