International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 2, 2011

Research Article

FORMULATION AND EVALUATION OF VALACYCLOVIR HYDROCHLORIDE MICROCAPSULES

B.PRADEEP*, M.NAGAMADHU, DAVID BANJI, B. BINDU MADHAVI, G. ARJUN, K.SHEKHAR

Department of pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda- 508001 Andhrapradesh, India
Email: pradeepkumar066@gmail.com

Received: 10 Nov 2010, Revised and Accepted: 14 Dec 2010

ABSTRACT

Valacyclovir hydrochloride loaded Ethyl cellulose microcapsules were prepared by the solvent evaporation technique. The process induced the formation of microcapsules with the incorporation efficiency of 80% to 90%. The effect of Ethyl cellulose concentration and conditions was evaluated with respect to entrapment efficiency, particle size, surface characteristics and in vitro release behaviors. Infrared spectroscopic study confirmed the absence of any drug - polymer interaction. Microcapsules matrices showing spherical surface, which was confirmed by scanning electron microscopy study. The mean particle size and entrapment efficiency were found to be varied by changing various formulation parameters. The *in vitro* release profile could be altered significantly by changing various formulation parameters to give a sustained release of drug from the microcapsules.

Keywords: Valacyclovir hydrochloride, Microcapsules, Drug release.

INTRODUCTION

Valacyclovir is L- valine 2[(2amino 1, 6 di hydro 6-oxo – 9H purin-9yl) methoxy] ethyl ester and exhibits antiviral activity against *Herpes simplex virus* and *Varicella zoster virus*. Valacyclovir exhibits similar potency but has more favorable pharmacokinetic characteristics, requiring less frequent dosing and achieving high blood plasma levels than acyclovir[1-3]. The metabolism of valicyclovir to acyclovir probably occurs within the gut lumen prior to absorption, in the small intestine after uptake but before entry in to the portal blood system and in the liver before entry in to the systemic circulation[4]. At pH higher than 4 valacyclovir underwent a base catalyzed reaction that lead to the active drug acyclovir and L-valine. The maximal stability was observed at pH under 4. At pH of 1.84, valacyclovir is only 2% hydrolyzed after a period of 24 hr. The prodrug was stable at low pH and rate of decomposition was accelerated at higher pH[5-7]. After oral administration Valacyclovir is rapidly converted to acyclovir and further phospharilated to acyclovir triphosphate. The incorporation of acyclovir tri phosphate into the growing chain of viral DNA results in chain termination[8-14].

Microencapsulation has been used in the pharmaceutical industry for the conversion of liquids to solids, taste masking of bitter drugs, acquiring prolonged or sustained release, reducing gastric irritation and environmental protection of labile moieties[15]. Microcapsules having core material and coating material. Core material is the drug substance which is to be coated by a coating material generally polymers are used. An important class of polymer mediated drug delivery systems that are applied for controlled drug delivery is the microcapsules[16, 17]. Microcapsules continue to be of much interest in controlled release based on relative ease of design and formulation and partly on the advantages of microparticulate system. Ethyl cellulose is a non biodegradable and biocompatible polymer used as encapsulating materials for the controlled release of pharmaceuticals[15].

The purpose of the present work was to prepare controlled release microcapsules of Valacyclovir hydrochloride using ethyl cellulose as a retarding material by applying the solvent evaporation technique. Drug to polymer concentration was altered to prepare microcapsules. These microcapsules were then evaluated for their drug entrapment efficiency and in vitro release profile. The physical characteristics were evaluated by scanning electronic microscopy, particle size and infrared spectroscopy.

Materials

Valacyclovir hydrochloride was obtained from Dr. Reddy's laboratories Ltd, Hyderabad. Ethyl cellulose, Methanol, n- hexane was procured from S.D.fine - chem. limited, Mumbai, Acetone was obtained from Universal laboratories private limited, Mumbai, Liquid paraffin was obtained from Accord labs, Andhra Pradesh, Span 80 was obtained from Central drug house private limited, Mumbai.

Method

Preparation of microcapsules[18]

paraffin that contained 1 ml of Span 80 as an emulsifier. The whole system was continuously stirred at 2,000 rpm for 5 h at room temperature. Acetone and methanol were then completely removed by evaporation, and the microcapsules were separated from the solution by vacuum filtration. The filtered microcapsules that formed were then washed three times with 50 ml of n-hexane to remove the residual paraffin oil and then collected, dried at room temperature overnight, and stored in a desiccator. Four different formulations with drug: polymer ratios (1:0.25, 1:0.5, 1:1, and 1:2) are prepared and coded as F1, F2, F3 and F4 respectively.[11]

Table 1: Formulae for different ratios of Valacyclovir hydrochloride microcapsules

Formulation Code	Drug: polymer (g)	Acetone (ml)	Methanol (ml)	Span 80	Liquid paraffin(ml)
F1	1:0.25	18	2	1%	100
F2	1:0.5	18	2	1%	100
F3	1:1	18	2	1%	100
F4	1:2	18	2	1%	100

Evaluation parameters

Drug polymer interaction (FTIR) Study

IR spectroscopy was performed on Fourier transformed infrared spectrophotometer (840, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr - press and the spectra were scanned in the wave number range of 4000 - 500 cm^{-1}. FTIR study was carried on Valacyclovir hydrochloride, physical mixture, formulations.

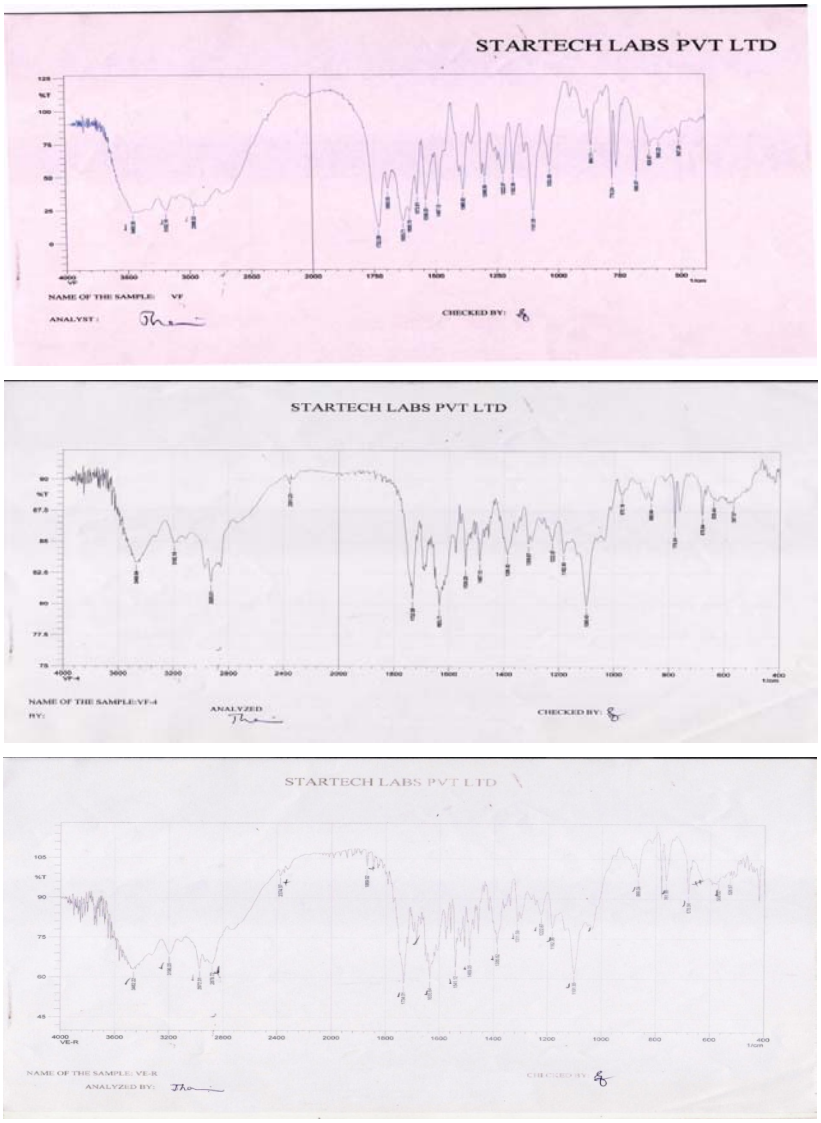

Fig.1: Valacyclovir pure drug, Valacyclovir with ethyl cellulose physical mixture, Valacyclovir with formulation

Scanning electron microscopy (SEM)

Scanning electron photomicrographs of drug loaded Ethyl cellulose microcapsules were taken by a small amount of microcapsules were spread on gold stub. Afterwards, the stub containing the sample was placed in the scanning electron microscopy (SEM) chamber. A scanning electron photomicrograph was taken at the acceleration voltage of 20 KV.

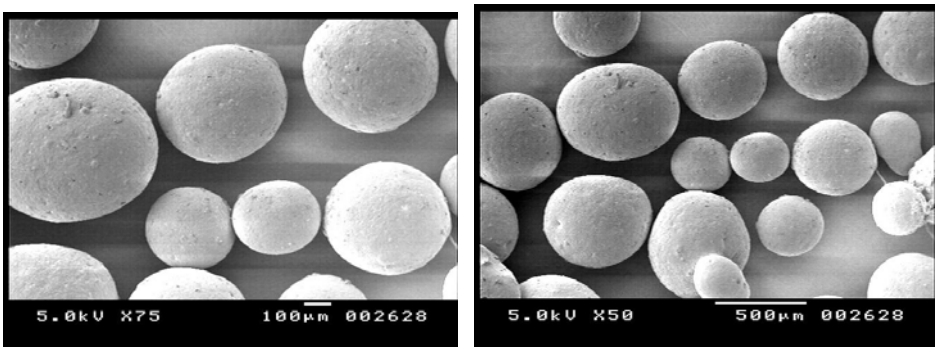

Fig.2: Scanning electron micrographs (SEM) of Valacyclovir hydrochloride microcapsules

Compressibility index

% Compressibility index = [1- V/V_o] ×100

Here V and V_o are the volumes of the sample after and before the standard tapping

Particle size measurement

The size of the prepared microcapsules was measured by the optical microscopy method using a calibrated stage micrometer for randomly selected samples of all the formulations.

Percentage yield

Percentage yield is calculated to know about efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of microcapsules recovered from each batch in relation to the sum of starting material. The percentage yield of prepared microcapsules was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Amount of microcapsules obtained}}{\text{Theoretical amount}} \times 100$$

Determination of Drug entrapment efficiency:

About 100 mg of accurately weighed, triturated drug loaded microcapsules were added to 100 ml phosphate buffer (pH7.4). The resulting mixture was placed in ultrasonicator for 10 min to complete dissolve of the drug. The solution was filtered using Whatman filter paper and 1ml of this solution was diluted and analyzed spectrophotometrically at 255 nm.

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Table 2: Percentage yield, encapsulation efficiency, Carr's index and average particle size of Valacyclovir hydrochloride microcapsules.

Batch Code	% yield	Encapsulation efficiency (%)	Carr's index	Average particle size (µm)
F1	94.4	90.21	13.6	423.33±1.52
F2	93.3	87.22	11.9	541.33±1.52
F3	92.5	84.60	9.9	613.33±1.52
F4	90.6	80.48	7.8	573.33±1.52

***In vitro* drug release**

Dissolution studies of Valacyclovir hydrochloride from microcapsules was performed according to USP basket type dissolution apparatus, the release study was performed in phosphate buffer of pH 7.4. The temperature was maintained at 37±0.5°C and the rotation speed was 100 rpm. An accurately weighed amount of microcapsules (Equivalent to 500mg of the drug) were added to the dissolution medium and at predetermined interval samples was withdrawn and replenished with an equal volume of fresh dissolution media. The drug content in the sample was analyzed spectrophotometrically at 255 nm.

Table 3: Cumulative % drug release values of different formulations

Time(hr)	F1	F2	F3	F4
1	37.24	35.00	31.04	22.28
2	48.40	44.18	37.10	31.38
3	55.60	52.05	47.00	36.29
4	69.70	65.05	55.60	45.32
5	81.02	76.57	66.87	60.87
6	83.04	80.55	69.43	63.17
7	90.30	86.27	79.25	67.75
8	92.20	88.16	81.69	75.77
9	95.37	90.30	85.94	78.19
10	96.78	92.60	89.51	85.47

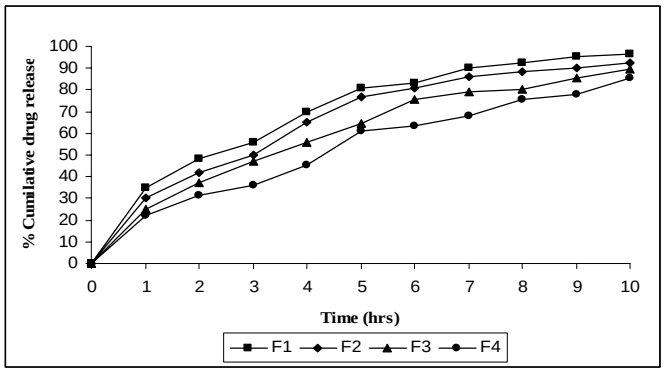

Fig. 3: *In vitro* drug release profile of different formulations of Valacyclovir hydrochloride microcapsules.

***In vitro* drug release kinetic studies[19]**

Data obtained from in-vitro release studies were fitted to various kinetic equations to find the mechanism of drug release from the Ethyl cellulose microcapsules.

Zero order model:

$Q_t = Q_0 + k_0 t$

First order model:

$Q_t = Q_0 e^{-k1t}$

Higuchi model:

$Q_t = Q_0 + k_H t^{0.5}$

Korsmeyer- Peppas model:

$Q_t / Q_\alpha = k_k t^n$

Where Q_t is the amount of drug released in time t

Q_0 is the initial amount of the drug

k_o is the zero order release constant

k_1 is the first order release constant

k_H is the Higuchi rate constant

k_k is the Korsmeyer- Peppas release constant and n is the release exponent that characterizes the mechanism of drug release.

Table 4: Diffusion exponent (n) of Peppas model and Regression coefficient (R^2) of Valacyclovir hydrochloride release data from microcapsules according to different kinetic models

Batch Code	Zero order	first order	Higuchi	Peppas model	n value
F1	0.8619	0.850	0.971	0.9832	0.463
F2	0.8782	0.842	0.965	0.9788	0.514
F3	0.9203	0.870	0.987	0.9927	0.566
F4	0.9547	0.918	0.981	0.9824	0.606

RESULTS AND DISCUSSION

In the present work controlled release microcapsules of Valacyclovir hydrochloride were formulated using Ethyl cellulose polymer by Solvent evaporation technique. Four batches prepared with different polymer ratios were shown in Table 1 and evaluated for physical properties like FTIR, SEM, particle size, Percentage yield, percentage drug content, encapsulation efficiency, *in vitro* dissolution, release kinetics of Valacyclovir hydrochloride microcapsules. The FTIR Spectra of Valacyclovir hydrochloride, physical mixture of Valacyclovir hydrochloride and Ethyl cellulose formulations are shown in the Fig 1. From this it is clear that the peaks at Alkane C-H stretch (2920.0), secondary amine N-H stretch (3446.6), aromatic C=C stretch (1602.7), tertiary amine C-N stretch (1363.6), ether –O- stretch (1288.4) cm^{-1} are present in both the pure, physical mixture and formulations without any change in their positions indicating no chemical interaction between Valacyclovir hydrochloride and polymers were shown in Fig 1. The Controlled release microcapsules of Valacyclovir hydrochloride prepared by Solvent evaporation were found to be almost spherical and free flowing. SEM was performed on the prepared microcapsules of 1:2 to access their surface and morphological characteristics as shown in Fig 2.

Percentage yield, encapsulation efficiency, Carr's index and average particle size were shown in Table 2. The maximum particle size range between 100 -600µm. Valacyclovir release from the microcapsules was studied for 10 hr, the drug released at constant rate in all these preparation and showed controlled release. The release of Valacyclovir hydrochloride in dissolution media (pH 7.4) is shown in Fig 3.

Data obtained for *in vitro* release studies was utilized for release kinetics. The co-efficient of determination indicated that the release data was best fitted with peppas model. Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of Korsemeyer Peppas model was found to be in the range of 0.5 to 1 indicating Non - Fickian of drug through Valacyclovir hydrochloride microcapsules were given in Table 4.

CONCLUSION

The present study is revealed that it is an appropriate method to encapsulate drug in to Ethyl cellulose shells because of good entrapment efficiency and sustained release behavior among the formulations are the result of the drug to polymer ratio employed. These results may suggest that potential application of Ethyl cellulose microcapsules as a suitable sustained release drug delivery system and it decreases the frequency of dosing and improve the patient compliance in the treatment of Herpes simplex virus and varicella zoster virus.

ACKNOWLEDGEMENT

The authors express their deep gratitude towards the Management and the Department of Pharmaceutics, Nalanda College of Pharmacy, Nalgonda, AP (India) for providing facilities to carry out this research.

REFERENCES

1. Ichiro Shinkai, Yukari Ohta: New drugs reports of new drugs recently approved by the FDA. Bioorganic & Medicinal Chemistry 1996; 4 : 1- 2.
2. Erik De Clercq: Antiviral drugs in current clinical use. Journal of Clinical Virology 2004; 30: 115–133.
3. Ganesh M, Narasimharao CV, Saravana Kumar A, Kamala kannan K, Vinoba M, Mahajan HS: UV Spectrophotometric Method for the Estimation of Valacyclovir HCl in Tablet Dosage Form. Journal of Chemistry2009; 6: 814-818.
4. Conan MacDougall, Joseph Guglielmo B: Pharmacokinetics of valaciclovir. Journal of Antimicrobial Chemotherapy 2004; 53: 899–901.
5. Gladys E Granero, Gordon L Amidon: Stability of valacyclovir: Implications for its oral bioavailability. International Journal of Pharmaceutics 2006; 317: 14–18.
6. Srinivasa Rao K, Sunil M: Stability indicating liquid chromatographic method for valacyclovir. International journal of chem. Tech. Research 2009; 1:702-708.
7. Manish Yadav, Vivek Upadhyaya, Puran Singhala, Sailendra Goswamia, Pranav S. Shrivastav: Stability evaluation and sensitive determination of antiviral drug, valacyclovir and its metabolite acyclovir in human plasma by a rapid liquid chromatography–tandem mass spectrometry method. Journal of Chromatography2009; 877: 680–688.
8. Beutner Karl R: Valacyclovir: a review of its antiviral activity, pharmacokinetic properties, and clinical efficacy. Antiviral Research 1995; 28: 281-290.
9. Bengi Uslu, Sibel A O zkana: Electro oxidation of the antiviral drug valacyclovir and its square-wave and differential pulse voltammetric determination in pharmaceuticals and human biological fluids. Analytical Chemical Acta 2006; 555: 341–347.
10. Maria Kasiari, Evagelos Gikas, Sofia Georgakakou, Michael Kazanis, Irene Panderi: Selective and rapid liquid chromatography/negative-ion electro spray ionization mass spectrometry method for the quantification of valacyclovir and its metabolite in human plasma. Journal of Chromatography 2008; 864: 78–86.
11. Ravi Kanneti, Ramadass Rajesh J. R. Aravinda Raj, Parloop A. Bhatt: An LC–MS–MS Method for the Simultaneous Quantitation of Acyclovir and Valacyclovir in Human Plasma. Chromatographia 2009; 70: 407-414.
12. Gerda Marie Friedrichsen, Weiqing Chen, Mikael Begtrup, Chao-Pin Lee, Philip L. Smith: Synthesis of analogs of L-valacyclovir and determination of their substrate activity for the oligopeptide transporter in Caco-2 cells. European Journal of Pharmaceutical Sciences 2002; 16: 1–13.
13. Patil1 GD, Yeole PG, Manisha Puranik, Wadher SJ:A Validated Specific Reverse Phase Liquid Chromatographic, Method for the Determination of Valacyclovir in the Presence of its

Degradation Products in Bulk Drug and in Tablet Dosage Form. International Journal of ChemTech Research 2009; 1: 16-26.

14. Jadhav AS, Pathare DB, Shingare MS: Development and validation of enantioselective high performance liquid chromatographic method for Valacyclovir, an antiviral drug in drug substance. Journal of Pharmaceutical and Biomedical Analysis 2007; 43: 1568–1572.
15. Nikhil k. Sachan, Bhupendra singh, Rama rao K. Controlled drug delivery through microencapsulation. Malaysian Journal of Pharmaceutical Sciences, 2006; 4: 65–81.
16. Hidekazu Yoshizawa. Trends in Microencapsulation Research, KONA, 2004; 22: 23-31.
17. Venkatesan P, Manavalan R, Valliappan K. Microencapsulation: A Vital Technique in Novel drug delivery system. Journal of Pharmaceutical. Science. & Research, 2009: 1: 26-35.
18. Satit Prasertmanakit, Nalena Praphairaksit, Worawadee Chiangthong, Nongnuj Muangsin: Ethyl Cellulose Microcapsules for Protecting and Controlled Release of Folic Acid. AAPS PharmSciTech 2009; 10: 1104- 1111.
19. Paulo Costa, Jose Manuel Sousa Lobo: Modeling and comparison of dissolution profiles. European journal of pharmaceutical sciences 2001; 13: 123-133.