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TESTING OF DRUG RELEASE FROM BIOADHESIVE VAGINAL TABLETS

Ayla Gürsoy and Ayşegül Bayhan
Department of Pharmaceutical Technology
Faculty of Pharmacy, Marmara University
80200 Nişantaşı, İstanbul, Türkiye

ABSTRACT

To establish an in vitro test method that can predict the drug release and dissolution behaviour of vaginal bioadhesive controlled release tablets, a system was developed and its appropriateness to the in situ conditions was examined. For this purpose, the dissolution rates of vaginal bioadhesive tablets were measured by three different methods. These were, USP dissolution apparatus two and a new vaginal dissolution tester (NVDT) which was developed by us with some modification of the vaginal tablet desentegration apparatus of BP 1988 and , testing in cow vaginas in situ. Four different bioadhesive tablet formulations were used being composed of the drug and the anionic polymer, polyacrylic acid (PAA) and the nonionic polymers, hydroxypropylmethyl

cellulose (HPMC) and ethylcellulose (EC). The release profiles of the in vitro and in situ methods were investigated and evaluated kinetically.

It was found that NVDT could be used to investigate the drug release from vaginal tablets.

INTRODUCTION

In recent years vaginal bioadhesive tablets have been developed as a new type of controlled release form for the treatment of both topical systemic diseases[1-4]. The greatest advantages of such bioadhesive tablets are the release of drug at a controlled rate and the possibility of maintaining them in the vagina for extended periods of time including the day hours and night, controversy to conventional vaginal tablets. They also enable lower dosing frequencies.

Among the polymers, poly(acrylic acid) (PAA) and hydroxypropylmethylcellulose (HPMC) are ideal exipients in vaginal bioadhesive tablet formulations, due to their high bioadhesive strength [5-9]. The main factors that govern the drug release rate over a predetermined time period from controlled release matrices are concentration of the polymer and the drug in the tablet, drug solubility and diffusion coefficient and matrix porosity and tortuosity [10-14].

To date standard dissolution tests for conventional tablets are the most widely used methods to investigate the release of drug from controlled release tablets and to provide the information on bioavailability [11,15-18].

From the data available up to now, no studies have been done to develope a special apparatus for in vitro dissolution of controlled release and/or bioadhesive vaginal tablets which give comparable results with in vivo or in situ experiments. The object of this work is to test such a possibility.

In the present study, therefore, tests of drug release from bioadhesive vaginal tablets were carried out using USP Dissolution Apparatus 2 paddle method [19] and the apparatus for disintegration of vaginal tablets described in BP and EP [20,21] with some modifications in the system. The results were compared with in situ data.

Since HPMC and PAA are hydrophilic [8,18,22] and bioadhesive polymers, a nonbioadhesive polymer EC was introduced into the formulations as a hydrophobic agent to control the swelling.

EXPERIMENTAL

Materials

Crystal violet (CV) (E. Merck, Darmstadt, RFA) was used as a model drug. The polymers were

poly(acrylicacid)(PAA)(Carbopol 934, B.F. Goodrich CO., Brecksville, OH, USA, Viscosity of its 0.5 % aqueous solution (pH=3.0) at 25 °C was 39400 mPas.), hydroxypropy(methylcellulose (HPMC) (Culminal MHPC 50, Aqualon GmbH und Co. K.G., DUsseldorf FRG, viscosity of a 2% aqueous solution at 20°C was 50 mPas), ethylcellulose (EC)(EC N-10 Hercules Incorporated Wilmington, Delaware 1984, USA, viscosity of a 5% aqueous solution at 25°C was 8-11 mPas), microcrystallincellulose (MCC)(Emcocel 90 M Edward Mendell Co. Inc. Finland), anhydrous lactose (Humko, Sheffield Chem., New Jersey 07071, USA), magnesium stearate (E. Merck Darmstadt RFA). The viscosities of all the polymers were reported as by the manufacturers.

METHODS

Preparation of Tablets

The bioadhesive vaginal tablets were prepared by direct compression according to the following formulations : (PAA:HPMC:EC) ; F1(10.0:44.0:44.3), F2(20.0:39.0:39.3) , F3(30.0:34.0:34.3) , F4(40.0: 29.0:29.3) and CV was 1.7 mg in each formulation. The drug and polymers were sieved and mixed for 5 minutes manually and compressed into tablets of 8.65 ± 0.03 mm diameter and 1.71 ± 0.08 mm thickness using a single punch tablet machine (Korsch EK-0, Berlin, Germany) fitted with flat-faced punches and with setting a hardness of 100 N. Tablets of 100 mg were obtained.

Conventional vaginal tablets were also prepared by direct compression and the formulation was 1.7% CV, 48.9% MCC, 48.9% anhydrous lactose, 0.5% magnesium stearate.

As the declared quantity of active ingredient in a single tablet is less than 5 mg, the tests of uniformity of content and tablet weight variation were determined according to USPXXII, NFXVII[19]. CV released in the dissolution medium was measured spectrophotometrically at 585 nm (Varian, Techtron Series 634).

Drug Release Studies

Two different in vitro methods and an in situ method were carried out for the drug release. Distilled water at 37±0.5 °C was used as dissolution medium throughout the in vitro studies. The results are the mean of ten tablets.

In Vitro Drug Release :

USPXXII, NFXVII Dissolution Tester [19].

The rotating paddle method was applied at 100 rpm, 50 rpm, 25 rpm and 12 rpm stirring rates.

New vaginal dissolution tester (NVDT)

Disintegration test of BP and EP [19,20] for vaginal tablets was applied after some modification of the test apparatus as shown in Fig.1 .

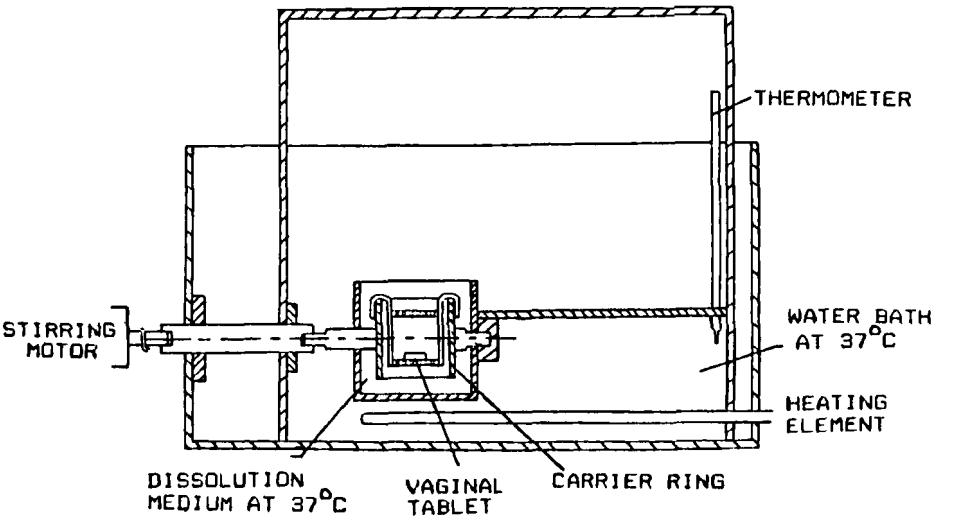

FIGURE 1
Schematic drawing of New Vaginal Dissolution Tester.

This apparatus contains two stainless steel discs each having 39 holes 4 mm in diameter, which are attached to a metal support by three hooks. A stirrer motor was connected and different rotating speeds were applied to the original system which was working manually. The vaginal tablet was placed on the bottom perforated plate and the plate assembly then clipped into the carrier ring. The cage was immersed in a 650 ml vessel containing the medium held at 37 ± 2 °C and rotated continuously at 25 rpm and 13 rpm and also a rotation every ten minutes as the original system.

In Situ Drug Release

These experiments were conducted using freshly slaughtered cow vaginas as described in our previous study [9]. Briefly, the tablet was placed in the vagina which was maintained at 37°C water bath. At certain intervals the amount of CV remaining in the tablet was assayed.

RESULTS AND DISCUSSION

Tablet Properties

Tablets meet the USPXXII, NFXVII criteria for weight variation and content uniformity. Four different types of tablet formulations were used to evaluate the effect of polymer ratio on drug release rate.

As shown in Fig.2 and Fig.3 among the tablet formulations, F4 tablet (PAA:HPMC:EC in the ratio 4:2.9:2.9) gave the optimum CV release rate after 6 hours in vitro and especially in situ conditions.

The ratio of the total polymer to drug was kept constant in all formulations, the only difference between formulations was in the ratio of anionic (PAA) to nonionic polymers (HPMC and EC). As the ratio increased the release of CV also increased which can be explained by the increased swelling of the matrix. Since PAA is a more hydrophilic polymer than HPMC, in general the tablets containing higher amounts of PAA swelled

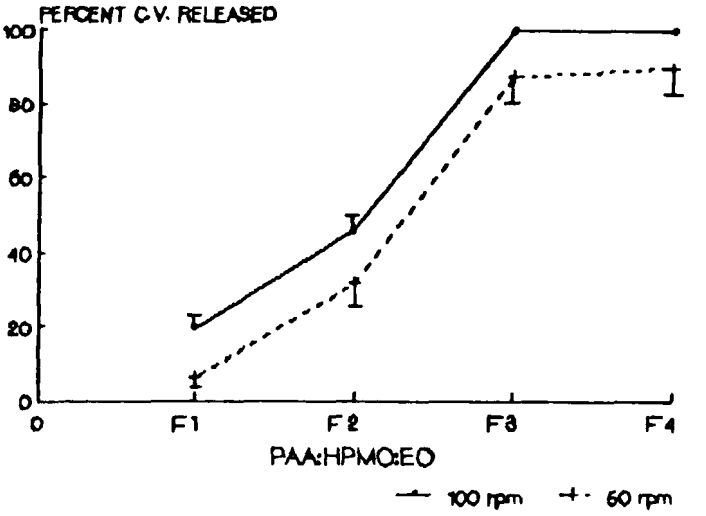

FIGURE 2

CV released, from tablets containing various ratios of polymers, according to USP method at the end of 6 h. Key: F1(1:4.4:4.4), F2(2:3.9:3.9), F3(3:3.4:3.4), F4(4:2.9:2.9). Vertical bars represent the standard deviation of the mean of 10 experiments.

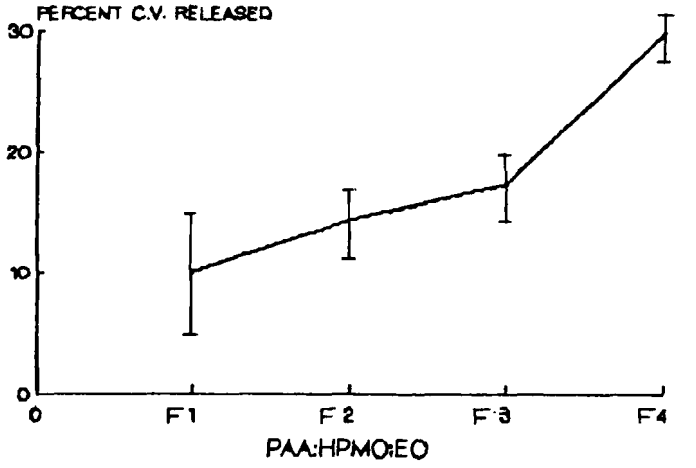

FIGURE 3

CV released from tablet formulations in cow vagina at the end of 6 h (in situ). Key: F1(1:4.4:4.4), F2(2:3.9:3.9), F3(3:3.4:3.4), F4(4:2.9:2.9). Vertical bars represent the standard deviation of the mean of 10 experiments.

faster. In a study of Ponchel et al. [8] the release of drug increased as the PAA content of the matrix increased and this phenomenon was explained by sweling behaviour of the HPMC/PAA systems. In another [16] it was shown that in a matrix tablet nonionic (HPMC) to anionic polymer (NaCMC) ratios significantly influence the erosion rate of matrix and consequently the shape of the release profile.

On the basis of our results, F4 tablet showed optimum drug release and was selected for the drug release studies for in vitro and in situ methods. When the F4 tablet was investigated using USP method [10] at 100 rpm, 50 rpm, 25 rpm and 12 rpm (Fig.4), it was found that the percent CV released increased as the rotating speed increased and the highest release was obtained at 100 rpm. As the rotating speed was increased the erosion rate of the tablet increased as well.

When NVDT was used (Fig. 5) it was found that with a rotating speed of 1r/10 min. the CV was released at a very slow rate and the total drug released after 6 h was only 10 % .However with a rotating speed of 13 rpm and 25 rpm the total released percentages were 26 % and 80 % respectively.

Our aim as stated was to find out a dissolution test system which would produce a release profile most comparable with in situ

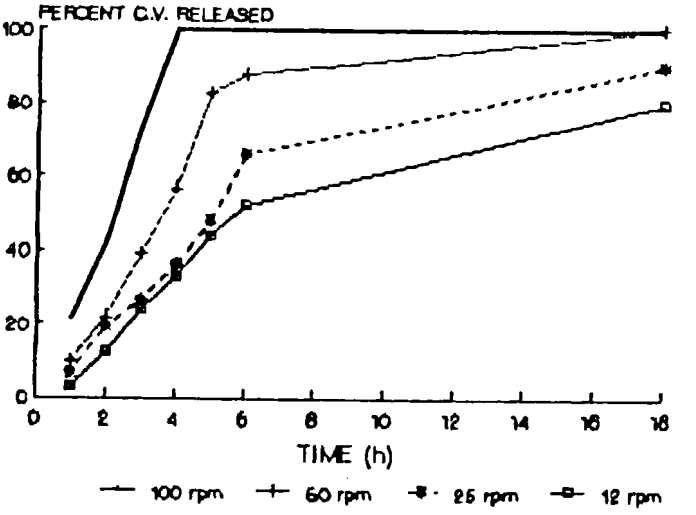

FIGURE 4
CV released from F4 tablet using USP method at various rotating speeds

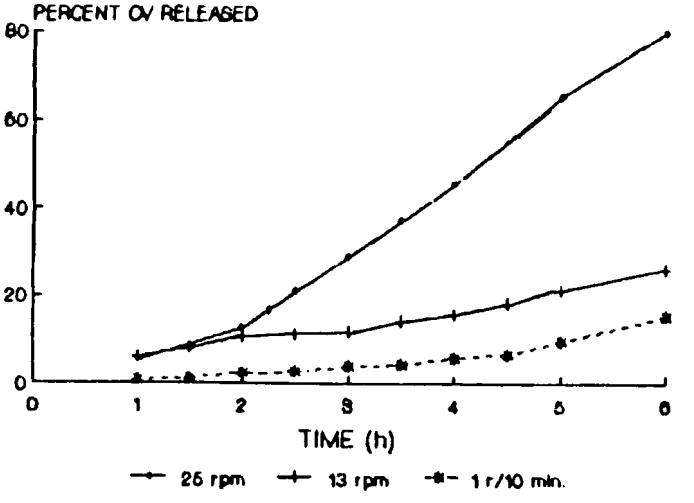

FIGURE 5
CV released from F4 tablet using NVDT at various rotating speeds

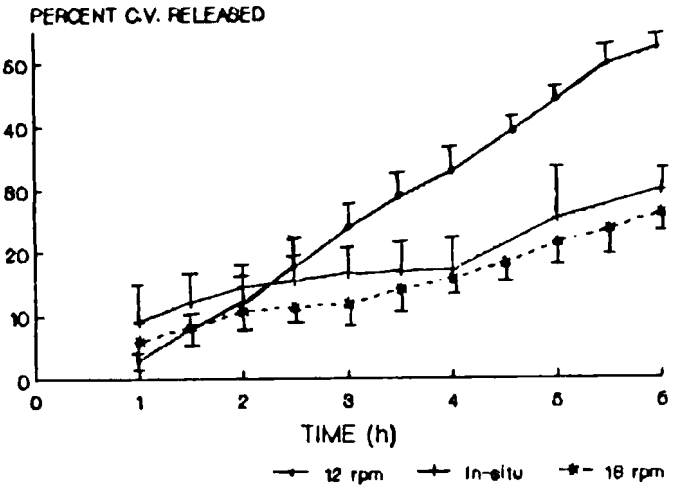

FIGURE 6
Comparison of percent CV released-time profiles of in situ, NVDT (13 rpm) and USP(12 rpm) method test results. Vertical bars represent the standard deviation of the mean of 10 experiments.

conditions. Also all the faces of the tablet were in contact with the vaginal mucosa in situ, the amount of drug released per time was a slow process. It was therefore decided to investigate low rotating speeds for in vitro systems. As shown in Fig. 6 the USP tester at 12 rpm produced a faster release rate than that in situ but the NVDT at 13 rpm showed nearly identical release profile to the in situ case.

On the other hand the applicability of the NVDT model to conventional CV vaginal tablets was also investigated. When these tablets were examined for their release behaviour in cow vagina

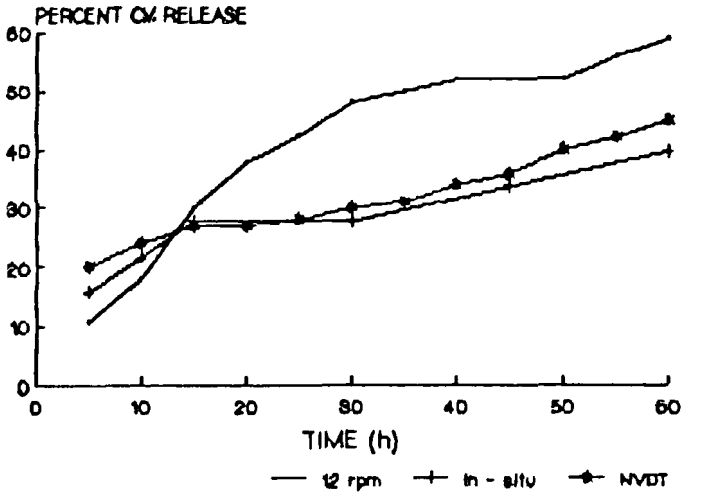

FIGURE 7
Comparison of percent CV released-time profiles of in situ, NVDT(13 rpm) and USP(12 rpm) method test results of conventional tablets.

in situ, it was found that CV release was 40 % in 60 minutes in (Fig.7). The release behaviour of this tablet by NVDT method correlate well with the release profile of in situ method indicating the suitability of NVDT method also to investigate the drug release from conventional tablets, whereas USP apparatus at 12 rpm gave rise to a faster release profile.

In order to investigate whether in situ and NVDT methods can distinguish minor formulation changes, the CV release rates of various bioadhesive tablet formulations (F1, F2, F3, F4 tablets) were tested. Fig.8 and Fig. 9 show that

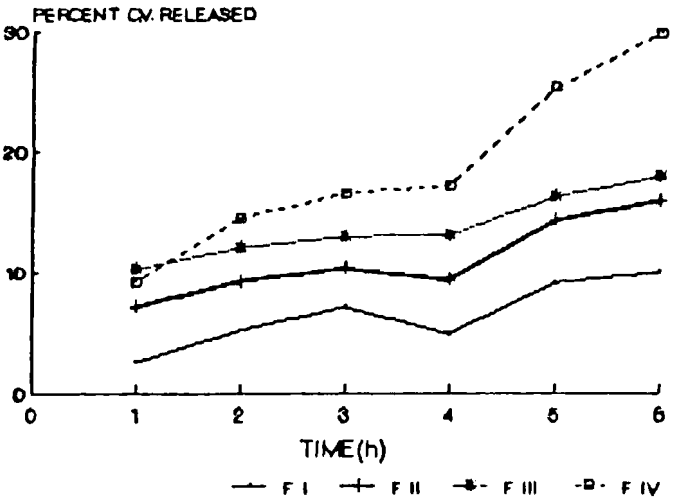

FIGURE 8
CV released from the tablet formulations in in situ conditions. Key : PAA:HPMC:EC ; F1(1:4.4:4.4), F2(2:3.9:3.9), F3(3:3.3:3.4), F4(4:2.9:2.9).

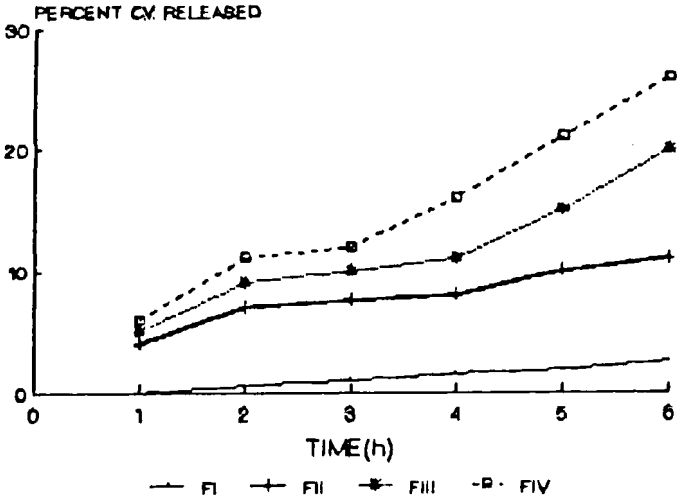

FIGURE 9
C.V released from the tablet formulations using NVDT. Key : PAA:HPMC:EC ; F1(1:4.4:4.4), F2(2:3.9:3.9), F3(3:3.3:3.4), F4(4:2.9:2.9).

for all four formulations the in situ and in vitro correlations were high.

Also further in vivo tests are required to confirm this, the in vitro NVDT system promises to be a good model in the field of drug release studies of vaginal tablets.

Kinetics of Drug Release

In general, in a matrix tablet formulation consisting of a hydrophilic polymers and a soluable drug the penetrating water will hydrate the polymer and dissolve the drug. Drug diffusion will commence after the dissolution of drug in the hydrated matrix medium, however formulation variations will affect this release rate.

It is generally believed that the drug release from a controlled release system should be at a zero order rate. It is reported that zero order release has not generally been observed till the entire drug is released since the rate of matrix swelling and attrition of the tablet surface are not equal, due to this the diffusional path length is not constant. For most of the hydrophilically swelling matrices the drug release varies as the square root of time [11,14,16,23-28].

CV release over 24 h is shown in Fig. 10. These data was kinetically studied. As shown in

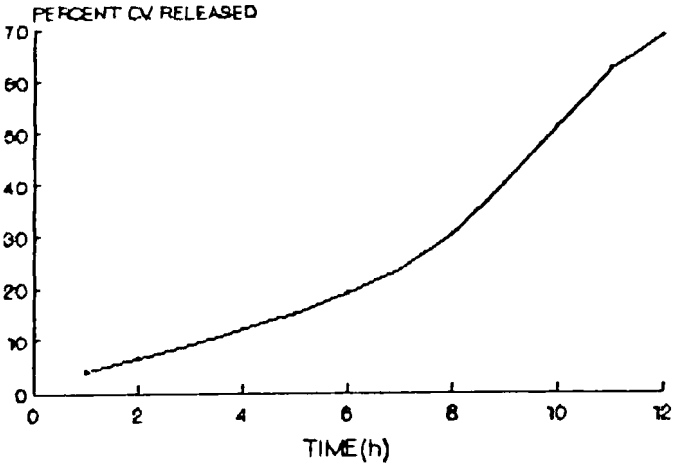

FIGURE 10
CV released from F4 tablet using NVDT over 24 h.

Fig. 10 by NVDT system F4 tablets had a nonlinear sustained release profile and the release was 80 % at the end of 24 h. In the first 6 h time a slow release rate of drug has been obtained. Since CV is only sparingly soluble, this slow diffusion commensed after the dissolution of the drug in the hydrated periphery of the tablet matrix. After 6 h the release rate increased, suggesting that a better hydration and swelling of matrix caused an increase in dissolution and diffusion of drug or both diffusion and attrition of the tablet surface caused a faster release rate between 6 h and 12 h. After this time the release started to increase slowly.

To examine the kinetic behaviour, the drug release data from NVDT experiments (Fig.10) were

TABLE 1

Statistical data from First-order, Higuchi-type and Zero-order plots of NVDT experiments giving the slope m_2 intercept C and coefficient of correlation r^2 for 12 hours time.

Release Kinetics	Slope m	Intercept C	Correlation Coefficient r^2
First-order	0.1405	0.3208	0.9695
Higuchi-type	3.1014	-31.4452	0.8042
Zero-order	5.8477	-11.3050	0.9121

fitted to the equation of Korsmeyer and Peppas (1983) [25] for $M_t/M_\infty \leq 0.7$

$$\frac{M_t}{M_\infty} = K\, t^n$$

The release exponent (n) value was found to be 1.3225 which indicates a non-Fickian release. The correlation coefficient (r^2) was 0.9462.

As shown in Table 1, by fitting the data of Fig. 10 for 12 h to the mean percent released versus square root of time relationship, zero order and first order kinetics, it was found that the release behaviuor could not be explained

exactly by any of them but showed a better fitting with first order kinetic with a correlation coefficient (r^2) of 0.9695, assuming that first order release was operative.

CONCLUSION

In conclusion new vaginal dissolution tester (NVDT) is a new approach to study the release behaviour of controlled release vaginal tablets.

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