Research Article

Effect of Timolol Maleate Concentration on Uptake and Release from Hydrogel Contact Lenses using Soaking Method

FURQAN A. MAULVI[1]*, TEJAL G. SONI[2], DINESH O. SHAH[3 & 4]

[1] Maliba Pharmacy College, Uka Tarsadia University, Surat 394350, Gujarat, India.

[2] Faculty of Pharmacy, Dharmsinh Desai University, Nadiad 387001, Gujarat, India.

[3] Shah-Schulman Center for Surface Science and Nanotechnology, Dharmsinh Desai University, Nadiad 387001, Gujarat, India

[4] Department of Chemical Engineering and Department of Anesthesiology, University of Florida, Gainesville, FL 32611, United States

ABSTRACT

This paper investigates the effect of timolol maleate concentration in soaking solution on uptake and delivery of drug through hydrogel contact lenses using soaking method for ocular drug delivery. Contact lenses were soaked in four different concentrations of timolol maleate (100 µg/ml, 200 µg/ml, 500 µg/ml and 1 mg/ml) for 12 hours. After the loading period, lenses were placed in vials containing 2 ml of simulated tear fluid and the release of drug into solution at 34°C was monitored for 24 hours. Contact lenses demonstrated significant uptake, but no significant effect was found on sustaining drug release and duration ($p > 0.05$) with increasing concentration of drug in soaking solution, confirmed by mathematical model and release kinetic data. Contact lenses were able to release the drug within therapeutic window for few hours only. Thus soaking method was not found to be effective for daily release through hydrogel contact lenses, suggesting the need for a novel technology to produce therapeutic contact lenses for daily use.

Keywords: Soaking method, Timolol maleate, Hydrogel contact lenses, Mathematical model.

1. INTRODUCTION

Currently, more than 90% of ophthalmic drugs are delivered through eye drops. This route of administration is inefficient due to low bioavailability to the corneal tissue because of rapid tear turnover, non-productive absorption in conjunctiva and nasal cavity, and low permeability of corneal epithelium [1]. The drug loss in the systemic circulation leads to drug wastage and potential side effects. Short drug residence time in tears results in a low corneal bioavailability of about 1–5% and rapid clearance, and hence requires frequent instillation of drops with large drug loadings to maintain the drug concentration within the therapeutic window [2, 3]. Several approaches have been explored to overcome the disadvantages of eye drops like the use of ointments, colloidal particles, inserts, collagen shields, in situ forming gels based on pH, temperature, ionic triggering, etc. [4-7]. However,

* **Corresponding author: Furqan A. Maulvi**, Maliba Pharmacy College, Uka Tarsadia University, Bardoli, Dist. Surat-394350, Gujarat, India.

E-mail: furqan.maulvi@utu.ac.in

Received: 02/06/2014, Accepted: 18/09/2014

most of these modifications prolonged the drug residence time to only a few hours with minimal increase in bioavailability. Thus, there is a need for a new drug delivery system for sustained drug delivery for at least few days; this led us to use contact lens for drug delivery.

In 2013, Baird's data suggest that the value of the worldwide contact lens market currently stands at roughly $7.6 billion, with the U.S. market valued at approximately $2.5 billion. This survey clearly states the increased usage of daily disposable soft contact lenses in global market [8]. The contact lens market globally comprises daily disposables (58%), soft frequent replacement lenses (8%), silicone hydrogels (28%), soft traditional lenses (2%) and rigid lenses (5%). The lenses are primarily utilized as devices for vision correction, but cosmetic and therapeutic usage of contact lenses have been explored by many researchers [8-10]. Due to its location in the immediate vicinity of the cornea, contact lenses have some unique advantages for delivering drugs to the cornea. The limited mixing in the post lens tear film between the lens and the cornea leads to a residence time of more than 30 min for drugs released from the lenses compared to about 5 min form eye drops. The enhanced residence time leads to significant increase in bioavailability, from 1 to 5% (from eye drops) to possibly as large as 50%, and thus reduces drug wastage [11, 12]. There have been a number of attempts in the past to use contact lenses for ophthalmic drug delivery based on soaking method [13-15]. The major problem of loading drug by this method is that the loaded drug diffuses out in a very short time of a few hours, which is inadequate for extended drug delivery applications.

Theoretical model (mathematically model) was applied to determine diffusion of drug from soaked contact lenses [16]. We considered the case in which the contact lenses are shaped like slab. The aspect ratio of the exposed surface diameter to the thickness is greater than 10, so we can assume diffusion is occurring in one dimension. The contact lens immersed in an aqueous environment, the concentration of the diffusing drug is negligible in the bulk fluid outside the contact lens. By application of Fick's Second Law and assuming the given initial and boundary conditions,

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial t^2}$$

$C(x, t) = C_0$ when $t = 0$

$\frac{\partial C}{\partial t} = 0$, while $t > 0$ and $x = 0$

$C = C_s$ while $t \geq 0$ and $x = \pm L/2$

We describe a system in which a planer contact lens undergoes one-dimensional diffusion over time in an environment in which the drug concentration is always effectively zero (sink condition is maintained), where C_0 represent the initial drug concentration (assumed to be uniform) in the homogeneous contact lens, x represent the distance from the central length-wise axis of the contact lens to the surface, C is the concentration of the drug within the contact lens at any given position and time. C_s is the concentration at the surface of the contact lens, D represents the constant diffusion coefficient which is independent of the position and concentration, t is time, and L is the thickness of the contact lens. At x= 0, the flux of the particles is effectively zero.

The solution is given by,

$$\frac{C - C_0}{C_s - C_0} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\left(\frac{(-1)^n}{2n+1} e^{\frac{-(2n+1)^2\pi^2 D}{4L^2}t} \cos\frac{(2n+1)\pi x}{2L}\right)$$

An effective way of comparing the release kinetics from different hydrogel sheets is to compare the fractional release of the drug at time t relative to the total drug released at infinite time, or M_t/M_∞. M_t is the total cumulative mass of therapeutic released at time t, and M_∞ is the total cumulative mass of therapeutic released at infinite time.

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2} e^{\frac{-(2n+1)^2\pi^2 D}{4L^2}t}$$

The above expression can be expressed in terms of error function.

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{L^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}} + 2\sum_{n=1}^{\infty}(-1)^n\, ier\, fc\left(\frac{nL}{2\sqrt{Dt}}\right)\right]$$

At short times ($M_t/M_\infty < 0.65$) the expression can be simplified to

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{\pi L^2}\right]^{1/2} \text{--------- (1)}$$

By plotting the fractional release of drug versus ($t^{0.5}/L$), we can calculate the diffusion coefficient from the slope. We can also measure how well the data matched a Fickian release profile by the empirical Power Law equation:

$$\frac{M_t}{M_\infty} = kt^n$$

$$\log\left(\frac{M_t}{M_\infty}\right) = k + n\, log(t) \text{ ------- (2)}$$

Using the drug release profiles and by plotting graph of log (M_t/M_∞) versus log (t), we can calculate diffusional exponent (n) from the slope and intercept is k. The constants, k and n, are characteristics of the drug-polymer system. By determining the diffusional exponent, *n*, one can gain information about the physical mechanism controlling drug release from a particular device. Based on the diffusional exponent, the drug transport in slab geometry is classified as Fickian diffusion, Case II transport, non-Fickian or anomalous transport, and Super Case II transport (Table 1). For systems exhibiting Case II transport, the dominant mechanism for drug transport is due to polymer relaxation as the gels swells. Anomalous transport occurs due to the coupling of Fickian diffusion and polymer relaxation [17].

Table 1: Drug transport mechanisms and diffusional exponents for hydrogel slabs

Diffusional exponent, *n*	Type of transport	Time dependence
0.5	Fickian diffusion	$t^{1/2}$
0.5 < *n* <1	Anomalous transport	t^{n-1}
1	Case II transport	Time independent
n > 1	Super case II transport	t^{n-1}

The objective of the paper was to investigate the application of soaking method in loading timolol maleate in hydrogel contact lenses for sustained drug delivery. The effect of timolol maleate concentration in soaking solution on uptake and release was determined using various mathematical models.

2. MATERIALS AND METHODS

2.1. Materials

Hydrogel contact lenses [poly hydroxyethyl methacrylate (Poly HEMA)] were provided by Leo lens technology (San Diego, California, USA). Timolol maleate was received as gift sample from Zydus Cadila Pharmaceuticals Ltd. (Gujarat, India). Ultra-pure water obtained by reverse osmosis (resistivity >18.2 MΩ cm; synergy U.V., Millipore, India) was used throughout the study. All the required chemicals were purchased from Sigma-Aldrich Chemicals (MO, USA).

2.2. Methods

2.2.1. Drug loading into the contact lenses by soaking method

The drug timolol was loaded in the contact lenses by soaking in 2 ml of timolol maleate solutions of varying concentration (100 µg/ml, 200 µg/ml, 500 µg/ml and 1000 µg/ml) in simulated tear fluid for 12 hours (previously optimized). Loading time was kept constant to evaluate the effect of drug concentration on uptake and in vitro drug release. At the end of the loading stage, the contact lenses were taken out and blotted to remove the excess drug solution from the surface, and subsequently used for the drug release experiments [18]. Batches were coded as TM100, TM200, TM500 and TM1000 for respective concentrations of 100 µg/ml, 200 µg/ml, 500 µg/ml and 1000 µg/ml. Uptake of drug by contact lenses were calculated by measuring the concentration of timolol maleate left in the soaking solutions after loading, using HPLC method at 295 nm [19].

2.2.2. In vitro release study (Flux study) in simulated tear fluid

The drug loaded contact lenses were placed in 2 ml of simulated tear fluid in glass vial (20 ml capacity) at 34° C in incubator with shaker at 100 RPM for 24 hours. The volume of the release medium was chosen to be 2 ml to approximately match the *in vivo* conditions of tear turnover. Samples of 100 µl of medium were withdrawn and replaced with the same volume of fresh simulated tear fluid for the release evaluation at time intervals of 1, 2, 4, 8, 12, and 24 hours, mimicking sink conditions. The content of drug was determined by HPLC method at 295 nm after suitable dilution. The release profile of drug was evaluated by plotting different graphs such as cumulative drug release (µg) versus time and percentage drug release versus time. The experiments were carried out in triplicate [15]. Benchmark release kinetic studies for diffusion coefficients (D) and diffusional exponents (n) were carried out according to the protocol described previously, using equations (1) and (2).

2.3. Statistical analysis

Each of the measured readings were compared to determine the level of significance between and within batches using SPSS programs (Version 21.0 for Window®, Chicago, IL) utilizing one-way ANOVA tests for multi-comparison.

3. RESULTS AND DISCUSSION

3.1. Drug uptake (loading) in hydrogel contact lenses

The amount of drug uptake (loaded) in the hydrogel contact lenses were calculated as the difference between the initial and final concentration of the soaking (loading) solutions for each individual batch. It was found that the concentration of drug in soaking solutions, significantly ($P<0.01$) affects the drug uptake in contact lenses, as listed in Table 2. Higher the concentration of drug in soaking solution, greater was the amount of drug loaded (uptake). This indicates that the higher drug loading in hydrogel contact lenses is possible by increasing the concentration of drug in soaking solution.

3.2. *In vitro* release of timolol maleate from hydrogel contact lenses

The cumulative (µg) and percentage timolol release from soaked hydrogel contact lenses are shown in figure 1 and 2 respectively. All the batches showed a rapid release of drug from soaked hydrogel contact lenses, as major amount of drug was released within 2 hours (Table 2). The amount of timolol maleate released during initial hours was greater (burst release), which indicates the release of adsorbed drug from the surface of hydrogel contact lenses. Later the drug released from the aqueous channels of hydrogel through diffusion. Timolol maleate is water soluble, this leads to a rapid diffusion of drug from the hydrogel contact lenses.

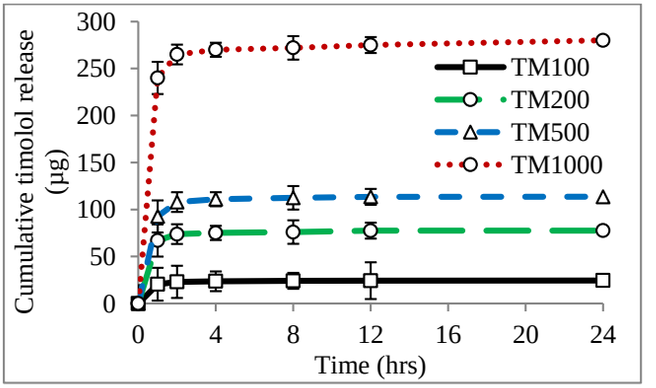

Figure 1: Cumulative release of timolol maleate during the 24-h release period from soaked contact lenses. Data is shown as mean ± SD (n=3).

The percentage drug released from the contact lenses at each time point is the calculated mean ± standard deviation of three replicates, and the total release is the sum of the individual time points. The in-vitro release results (% release) at each time point were analyzed using SPSS software. It was found that the percentage release of drug from hydrogel contact lenses with time is independent ($P>0.05$) of the amount of drug loaded, by varying drug concentration in soaking solution. All batches under test displayed the same general pattern of drug release over time (figure 1 and 2). The drug loaded lenses showed a burst release during initial hours. No further significant amount of drug released after 2 hrs (i.e. no sustained release was observed).

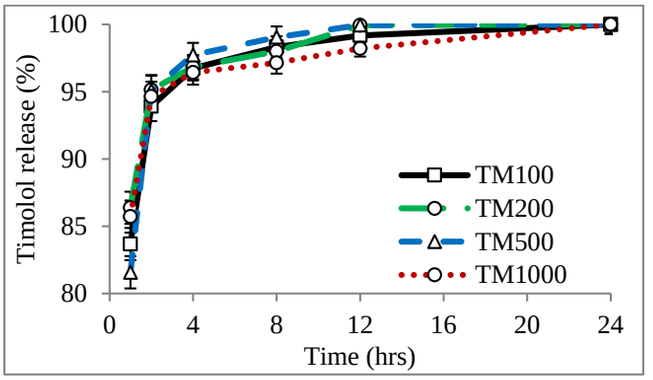

Figure 2: Percentage release of timolol maleate during the 24-h release period from soaked contact lenses. Data is shown as mean ± SD (n=3).

The figure 1 suggests that as the concentration of drug in the soaking solution increases (from batch TM100 to TM1000), higher drug uptake and release amount were observed. But no significant enhancement in release duration was observed (sustained release) at all-time points (P>0.05) when the concentration of drug in soaking solution was varied. The results clearly point out the limitation of soaking method for ocular drug delivery for water soluble drug like timolol maleate.

To understand the mechanism of drug release, it was informative to compare the release profile with diffusion controlled model. Percentage release profiles for first 4 hours fitted to Eq. (1) and (2) gave diffusion coefficient values and release exponents n and k (Table 3). The calculated diffusion coefficient (considering average thickness of hydrated contact lens = 100 µm) for TM-100, TM-200, TM-500 and TM-1000 were 8.538×10^{-9}, 5.401×10^{-6}, 8.356×10^{-6} and 4.285×10^{-6} mm^2/sec and the diffusional exponents (n) were 0.104, 0.087, 0.129 and 0.079 respectively. Diffusion coefficient varies slightly (non-significantly, $p > 0.05$) among batches, suggesting no change in release rate on increasing the concentration of timolol in soaking solution. The diffusional exponents ($n < 0.5$) indicate diffusion controlled fickian release of drug from aqueous channels of contact lenses for all the batches. Higher values of intercept k, indicate low affinity of drug to hydrogel polymer matrix, and no change ($p>0.05$) in k, indicates that there is no change in affinity between drug and hydrogel polymer matrix for all batches [16].

Table 2: Effect of soaking solution concentration on uptake and release of timolol maleate from hydrogel contact lenses

Batch code	Soaking solution concentration (µg/ml)	Drug uptake by contact lenses (µg) ± SD	Total drug released after 2 hours (µg) ± SD	Percentage drug released after 2 hours ± SD
TM100	100	24.50 ± 1.15	23.01 ± 1.21	93.92 ± 0.81
TM200	200	77.57 ± 1.25	73.80 ± 1.41	95.14 ± 0.91
TM500	500	113.58 ± 1.54	108.00 ± 1.71	95.09 ± 0.71
TM1000	1000	280.00 ± 0.93	265.11 ± 1.01	94.64 ± 0.51

Data are presented as mean ± SD (n = 3).

Table 3: Release kinetic parameters obtained by applying mathematical model

Batches	Diffusion coefficient (D = mm^2/sec)	Regression coefficient (R^2)	Diffusional exponent (n)	Intercept (k)
TM100	8.538×10^{-9}	0.904	0.104	1.930
TM200	5.401×10^{-6}	0.875	0.087	1.940
TM500	8.356×10^{-6}	0.876	0.129	1.922
TM1000	4.285×10^{-6}	0.821	0.079	1.941

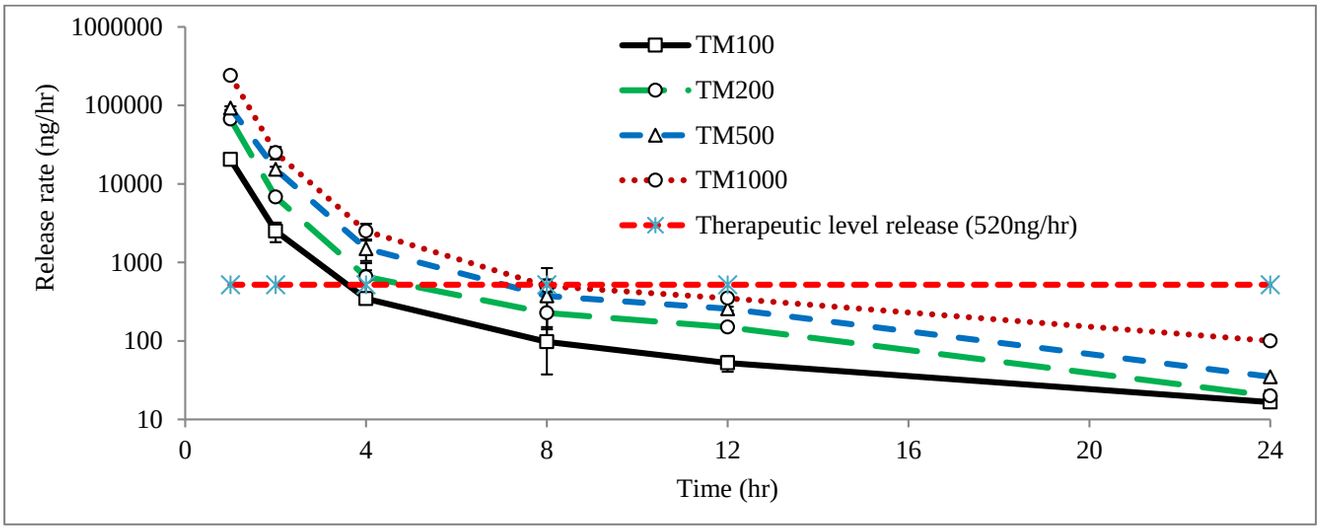

Figure 3: Release rate of timolol maleate during the 24-h release period from soaked contact lenses. Data is shown as mean ± SD (n=3).

The question will always remain, whether soaking method can be used effectively to produce therapeutic contact lenses for ocular drug delivery for water soluble drug like timolol maleate. The recommended dosage schedule, when using a 0.125%w/v timolol maleate ophthalmic solution is two drops per eye per day or 12.5 µg/day or 520 ng/hr (considering 5 % absorption in case of eye drops). Batches TM-100, TM-200, TM-500 and TM-1000 released the drug within therapeutic level (520 ng/hr) for 3 hr, 4.5 hr, 7 hr and 8 hr respectively (figure 3). As the concentration of drug in soaking solution increases, the drug uptake increases, which led to higher amount of drug release. But the release duration was not extended proportionally or significantly. None of the batch releases drug for 24 hours to enable its use for daily disposable therapeutic contact lenses. Limitations of soaking method would seem to prevent this drug delivery system to be used with extended wear contact lenses because after its initial burst release there would be no further release to maintain its concentration above therapeutic levels for days.

4. CONCLUSION

This study suggests that there is no significant enhancement in release duration (sustained release), when the concentration of timolol maleate in soaking solution was varied. It also shows the limitation of soaking method for ocular drug delivery through hydrogel contact lenses for water soluble drug like timolol maleate.

5. ACKNOWLEDGMENTS

The authors are thankful to the LeoLens technology, California, USA for supplying hydrogel contact lens and Principal, Maliba Pharmacy College, Gujarat, India for providing facilities to carry out the work.

6. REFERENCES

1. Lang JC. Ocular drug delivery conventional ocular formulations. Advanced Drug Delivery Reviews. 1995;16(1):39-43.
2. Le Bourlais C, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems - Recent Advances. Progress in retinal and eye research. 1998;17(1):33-58.
3. Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discovery Today. 2008;13(3):144-151.
4. Ma W-D, Xu H, Wang C, Nie S-F, Pan W-S. Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system. International Journal of Pharmaceutics. 2008;350(1):247-256.

5. Srividya B, Cardoza RM, Amin P. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. Journal of Controlled Release. 2001;73(2):205-211.
6. Xiong W, Gao X, Zhao Y, Xu H, Yang X. The dual temperature/pH-sensitive multiphase behavior of poly(N-isopropylacrylamide-co-acrylic acid) microgels for potential application in in-situ gelling system. Colloids and Surfaces B: Biointerfaces. 2011;84(1):103-110.
7. Ibrahim H, Bindschaedler C, Doelker E, Buri P, Gurny R. Concept and development of ophthalmic pseudo-latexes triggered by pH. International Journal of Pharmaceutics. 1991;77(2):211-219.
8. McNamara NA, Polse KA, Brand RJ, Graham AD, Chan JS, McKenney CD. Tear mixing under a soft contact lens: Effects of lens diameter. American Journal of Ophthalmology. 1999;127(6):659-665.
9. Creech J, Chauhan A, Radke C. Dispersive mixing in the posterior tear film under a soft contact lens. Industrial & Engineering Chemistry Research. 2001;40(14):3015-26.
10. Zhu H, Chauhan A. Effect of viscosity on tear drainage and ocular residence time. Optometry & Vision Science. 2008;85(8):715-725.
11. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. Journal of Controlled Release. 2013;165(1):82-89.
12. Peng C-C, Burke MT, Carbia BE, Plummer C, Chauhan A. Extended drug delivery by contact lenses for glaucoma therapy. Journal of Controlled Release. 2012;162(1):152-158.
13. Soluri A, Hui A, Jones L. Delivery of ketotifen fumarate by commercial contact lens materials. Optometry & Vision Science. 2012;89(8):1140-1149.
14. Xu J, Li X, Sun F. In vitro and in vivo evaluation of ketotifen fumarate-loaded silicone hydrogel contact lenses for ocular drug delivery. Drug Delivery. 2011;18(2):150-158.
15. Karlgard C, Wong N, Jones L, Moresoli C. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. International Journal of Pharmaceutics. 2003;257(1):141-151.
16. Yañez F, Martikainen L, Braga ME, Alvarez-Lorenzo C, Concheiro A, Duarte CM, et al. Supercritical fluid-assisted preparation of imprinted contact lenses for drug delivery. Acta Biomaterialia. 2011;7(3):1019-1030.
17. Shi D. Biomedical devices and their applications: Springer; 2004. 18-25.
18. Kim J, Chauhan A. Dexamethasone transport and ocular delivery from poly (hydroxyethyl methacrylate) gels. International Journal of Pharmaceutics. 2008;353(1):205-222.
19. Peng C-C, Burke MT, Chauhan A. Transport of topical anesthetics in vitamin E loaded silicone hydrogel contact lenses. Langmuir. 2011;28(2):1478-1487.