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Intraocular Pressure Model Predictive Control: A Simulation of Circadian and Mean Intraocular Pressure Control

Omer Hamid

Abstract- ***Pharmacokinetics/Pharmacodynamics (PK/PD) models of four ophthalmic drugs taken from the literature, employed in building model predictive control (MPC) systems. The drugs are: Latanoprost, Bunazosin, Timolol, and PF-04475270. MPC successfully controlled the mean intraocular pressure (MIOP) to a set point without overshoot or noticeable steady state error. The drug model representation order is vital in the suppression of circadian intraocular pressure variation, while the mean intraocular pressure is controllable irrespective of the model order.***

Index Terms:- glaucoma, intraocular pressure, Circadian pattern, model predictive control, pharmacokinetics/ pharmacodynamics.

I. INTRODUCTION

Impairment of the draining system of eye aqueous humor results in accumulation of fluids in the eye that increases the intraocular pressure (IOP), which in turn can cause irreversible damage to the optic disc and a permanent loss of sight. Increased IOP is a risk factor for the development of glaucoma [1]. Most eye medications are in solution forms and wasted during applications due to reflex, eye tearing or missed drops. Pilocarpine, a glaucoma drug, as an example has a bioavailability less than 5% [2] when applied topically on the eye. Glaucoma control via medications can be viewed as an open loop control system. Pulsatile drug delivery technologies in other areas of medicine were reviewed by Deepika Jain *et* al.[3], taking in mind the circadian rhythm in humans. These pulsatile drug delivery systems release drugs in controlled stimulated manner but still act as open control systems. Drug delivery systems (as ocular inserts) capable of increasing the drug bioavailability and resident times were reviewed in [4], Molteno [5] in 1969, invented a glaucoma drainage device (GDD) made from a tube inserted into eye anterior chamber and drains into sub-conjunctival plate in response to an increase in IOP. The Ahmed Glaucoma (AGV), an improved GDD [6], was available in 1996. These GDD devices have an element of closed loop concept, but they are invasive and used as a last glaucoma treatment option. Gedde *et al*. reviewed GDD devices versus trabeculectomy [7], and found a surge in GDD use. Invasive closed loop control system using a fluid pump was patented in [8]. Up-to-date, there is no system that can control IOP automatically and noninvasively. Earlier this year, simulation of IOP automatic control system was presented [9]. There is a long way of bringing these simulation ideas to practice, but they will shed light on the feasibility of system hardware implementation. Any attempt shall be made in the future of designing non-invasive IOP control, must address, IOP sensors, means of applying the drug, and an impeded system for the controlled release of the drug. Daniel Piso et al. reviewed IOP sensing devices [10] and one of the promising available IOP sensors is a wireless Contact Lens Sensor (CLS) [11] which produces a voltage signal relative to the IOP. In closed loop IOP control system, the drug must be released on demand and with certain magnitude. Many researchers tackled the problem of ophthalmic drug bioavailability and resident time [12],[13]. Mohammadi *et al*. 2014 [14] experimented with Latanoprost soaked silicon hydrogel contact lens that showed extended drug delivery time. Gause *et al*. showed that drug-soaked contact lens increases the bioavailability by 50% compared to 5% bioavailability of eye drops [15]. Hydrogel contact lens could be the right candidate for controlled released of ophthalmic drugs in the future. Murdan in 2003, reviewed electro-responsive hydrogels, where electric pulses can release controlled amount of drugs [16]. Hydrogels can respond to other stimuli like temperature, pH, ultrasound and most importantly (for ophthalmology) to light as reviewed by Singh [17]. Near infrared pulses are utilized in pulsatile release of reagents from deformation-free hydrogel materials [18]. In this article, we assume the existence of an IOP sensor and a controlled stimulated drug release. The eye IOP and its response to ophthalmic drugs can be viewed as a dynamic system model. The parameters of this model are derived from the Pharmacokinetics/Pharmacodynamics PKPD drug representations. Sakanaka *et al* [19] reported the modeling of PKPD of rabbits' eyes for the drug Bunazosin (α1-blocker), in 2004, which reduces IOP by increasing the uveoscleral flow. Sakanaka *et al* [20] in 2008, obtained a PKPD model of Timolol (β-blocker) in rabbits, the model is simulated using MULTI (RUNGE) program, Timolol is a lipophilic drug used in the treatment of open-angle glaucoma. Kenneth *et al* (2009) [21], obtained a PKPD model of CP-734432 after a topical administration of PF-04475270 drops to dogs' corneas, the model is implemented using NONMEM software. PF-04475270 is a prodrug of CP-734432, lowers IOP by increasing the trabecular outflow facilities while Timolol inhibits aqueous humour production, this different mechanism leads to different models. Luu *et al*. [22] formulated a model for Latanoprost that takes into consideration IOP circadian variation and dosing time. Latanoprost is a lipophilic prostaglandin analog that lowers IOP by increasing uveoscleral outflow.

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***** Correspondence Author (s)
Omer Hamid*, Department of Medical Equipment Technology, College of Applied Medical Sciences, Prince Sattam Bin Abdul-Aziz University, Alkharj, Kingdom of Saudi Arabia. Alkharj, 422.

In 2014 Durairaj *et al*. develop a PKPD a Latanoprost model that predicts and control diurnal IOP in patients [23].

Intraocular pressure varies during a 24 hour period. Fogagnolo *et al*. [24] showed that IOP circadian fluctuation in healthy young subjects was 7.3±3.2 mm Hg and was higher in patients with glaucoma (9.3±3.2 mmHg). Agnifili *et al*. in 2015 [25] examined the circadian intraocular pressure patterns in healthy subjects and patients and reported a nocturnal acrophase using a CLS; Sensimed Triggerfish Lausanne, Switzerland. Such slow circadian pattern put more constraints on the design of automatic IOP system, the topic of this article which is a continuation of the work in [9]; here two more ophthalmic drugs are explored. All the reviewed glaucoma ophthalmic drugs delivery systems are either wasteful, open control systems or invasive in nature. In this article four drugs, PKPD models taken from the literature were used to simulate automatic closed loop IOP control systems that provide demanded size of eye drops that keep IOP at set points in the presence of circadian rhythm.

IOP automatic control systems could benefit subjects vulnerable to acute glaucoma attacks and improve ophthalmic drugs instillation.

II. METHOD

Similar to the method described in [9]. Four ophthalmic drugs, namely Latanoprost Bunazosin, Timolol and PF-04475270 and their PKPD models are employed in the design of closed IOP control systems. The eye and the way it interacts with a drug results in a system described by a set of differential equations given in [19] – [22].

A program was written in Matlab (ver. 2012) environment to convert the differential equations to a state space model. A model predictive controller is built and a closed loop model predictive control system is designed and simulated for each of the four drugs. Here is a summary of the steps followed in this article:

i- Build a Matlab function for each drug model that contains a set of time domain differential equations.

ii- For each drug call the function to form a nonlinear grey-model to represent the drug; by invoking 'idnlgrey' instruction.

iii- Simulate the model-grey box and form an input/output data set. The input is a train of pulses representing multiple eye drops. The outputs are the time course drug amount in the tear film, cornea, aqueous humour, iris-ciliary body, and the IOP response. The IOP is taken as the only intended output response.

iv- Estimate a state space model from the data set, with 'ssest' Matlab instruction that results in A, B, C matrices (see equations 1, and 2 below).

v- Convert the model to a discrete system.

vi- Form a model predictive controller.

vii- Design and simulate a closed loop model predictive control system for each drug; with different control constraints.

The estimated state space model (step iv) for each drug has the following form:

$$dx/dt = A\,x(t) + B\,u(t) \quad (1)$$

$$y(t) = C\,x(t) \quad (2)$$

where x is the system state vector, y the output vector, u the plant input, A, B and C are state space matrices whose elements are related to the drug rate constants, elimination coefficients and IOP pharmacodynamics parameters. There is no direct feed-through so that D is considered zero. The number of space states depends on the drug model.

Latanoprost is modeled using transit compartments [22], which makes it possible to represent it, in this article, by three and then seven states (compartments). This is needed to investigate the effect of model order in IOP response. The other three drugs' models were based on conventional time lag compartmental modeling and there is no room for changing the order number. The above model (eq. (1),(2)) describe the actual plant for the control system. The state matrices A, B, C and D are used to build the controller. There is only one input u (eye drops) produced by the drug reservoir, and only controlled output, the IOP as shown in Fig. 1. The single feedback control signal is derived from IOP, supposed to be generated by a CLS, and applied to the controller input as shown in Fig. 1. The controller produces a signal that stimulates the drug reservoir to produce u(t), the magnitude of u(t) steers IOP towards IOP Ref. set point. The drug reservoir could be a hydrogel drug-loaded contact lens [18], that releases a drug in response to a light stimulant. In this research, it is assumed that the drug reservoir has a linear response, zero time delay, and gain equal to one. The controller impeded system realization and the light source could be attached to a frame of eyeglasses. The four drugs IOP responses are examined for circadian rhythms suppression under closed loop control and also for mean IOP automatic control. The 24 hour IOP circadian signal starting at 8:00 am is shown in Fig. 2, its math expression is given in [22],[23].

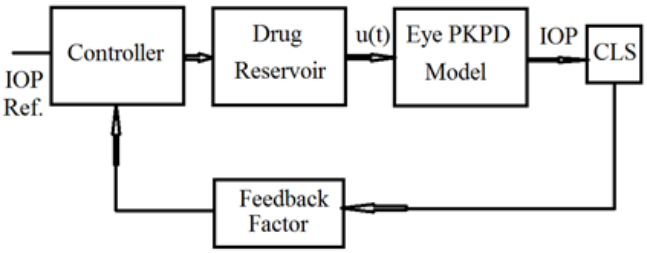

Fig. 1 A block diagram of an automatic IOP control system.

III. RESULTS AND ANALYSIS

Closed loop model predictive control systems' results are presented and analyzed here with some *illustrations. The drugs' systems are simulated to lower the IOP from 24 mmHg to 14 mmHg as in the case of Latanoprost,* Bunazosin, *and Timolol; PF-04475270 system lowers IOP from 100% to 80% of its initial value. The general structure of the closed loop control systems software looks the same but model predictive control constraints differ from one drug to another.*

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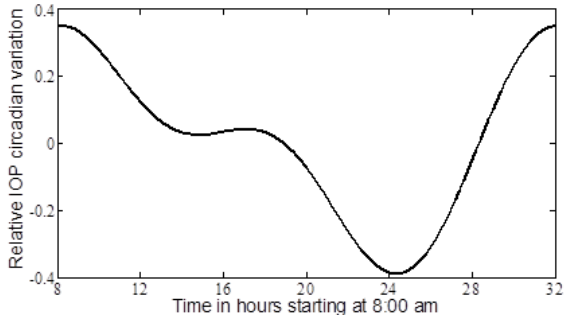

Fig. 2 IOP circadian pattern in 24 hours.

A. *Latanoprost*

Latanoprost transit compartment model allows order number changing by changing the number of compartments with ease. This is not possible with the other mentioned drugs. A lower order system is cost effective in terms of implementation and hardware components. A third order closed loop model predictive Latanoprost system simulation resulted in a trace shown in Fig. 3, after a single dose per day. As shown the system was not able to eliminate the circadian periodic disturbance but was able to achieve the mean IOP (MIOP) set point of 14 mmHg after a week of daily dosing.

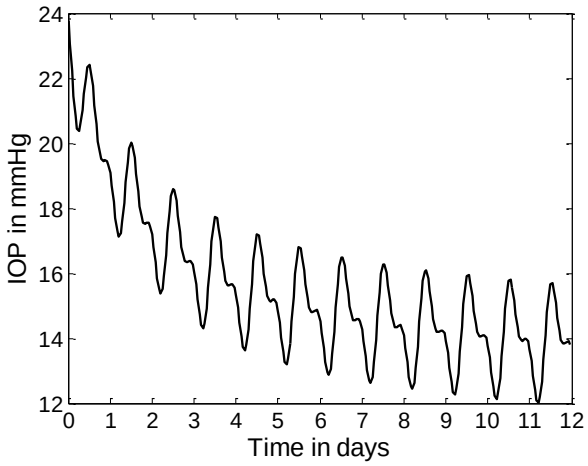

Fig. 3 Latanoprost 3rd order IOP system response.

The controller output is shown in Fig. 4, it tries to deliver drug amounts necessary for circadian IOP control. The time of drug delivery (morning/evening) seems to have no effect when the circadian signal is shifted in time with respect to the pulses simulating the drug drops.

A seventh order closed loop model predictive Latanoprost system simulation resulted in a trace shown in Fig 5, after a single dose per day. As shown the system has successfully eliminated the circadian disturbances to a great extent and reached a MIOP of 14 mmHg after a week of daily dosing. The seventh order controller is designed to produce an output, shown in Fig. 6, that drives IOP towards 14 mmHg and simulates a controlled pulsed hydrogel drug delivery system.

The third order system failure to eliminate the circadian rhythm can be explained by the fact that higher order systems have a steeper frequency response in the stop band. The third order system has succeeded in controlling the MIOP as it is a slow process. The closed loop 7th order system IOP output (see Fig. 5) behaves as a low pass system that eliminates disturbances. The fundamental frequency of the circadian pattern is 11.57 µHz and was not able to pass through the 7th order system. These drugs' systems then can be said to operate in sub micro-Hertz frequency ranges.

A controlled continuous dosing eliminates ripples that are noticed in pulsatile daily dosing (see Fig. 5). Fig. 7 shows a smooth descent of IOP due to a controlled continuous drug release from the assumed reservoir. The set point is reached two days earlier compared to pulsed daily delivery.

Latanoprost 7th order control systems are stable, the poles of the characteristic equations of matrix A (see equation 1), lie on the left-hand side of the complex frequency domain as given below:

-0.1661 + 0.0120i, -0.1661 - 0.0120i, -0.1454 + 0.0142i, -0.1454 - 0.0142i, -0.1380, -0.0046, and 0.0000

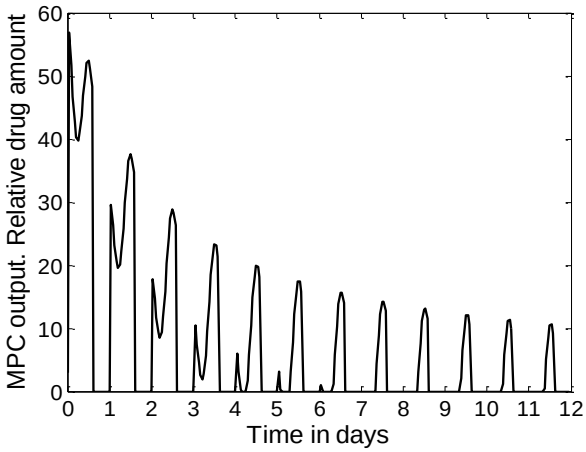

Fig. 4 MPC output for three order system.

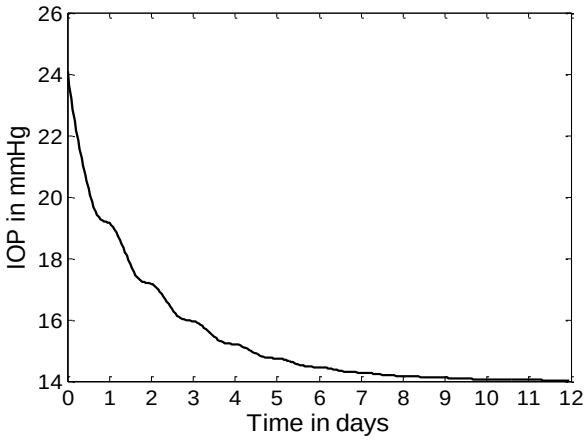

Fig. 5 Latanoprost 7th order IOP daily dose control.

B. *Bunazosin*

Bunazosin plant has nine states, resulting in a nine order system. The simulation of its closed loop model predictive control system disturbed with a circadian pattern, resulted in IOP trace shown in Fig. 8. The drug is administered twice a day and has effectively removed the circadian IOP variations due to the high order and sub-micro Hertz behavior of its plant model. The IOP set point was 14 mmHg.Fig. 9 shows Bunazosin MPC output as it tries to adjust the IOP at the set point. There is no room for changing the model order as we did for Latanoprost, Bunazosin is modeled using time lag compartmental modeling .

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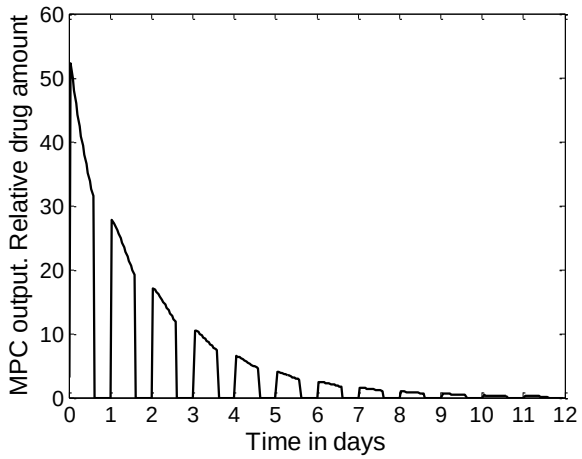

Fig. 6 Latanoprost 7th order system MPC output.

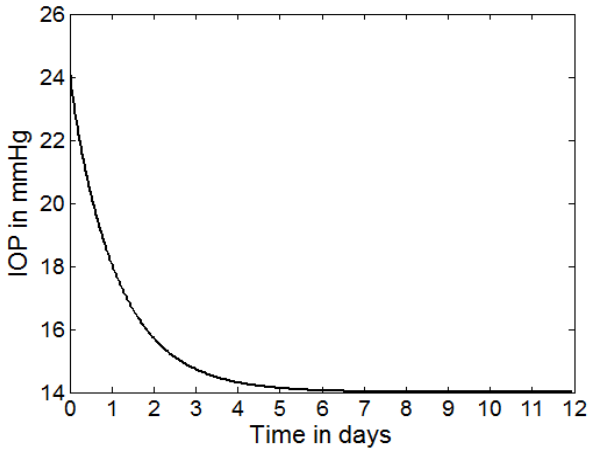

Fig. 7 Latanoprost 7th order continuous dose IOP control.

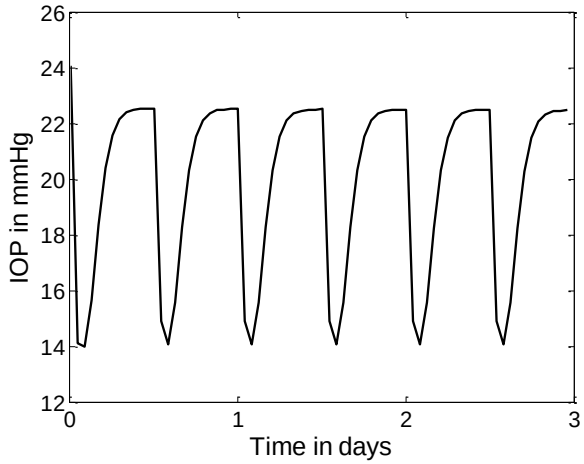

Fig. 8 Bunazosin IOP response.

The Bunazosin plant is stable as the characteristic equation of matrix A, has nine poles on the left hand side of the complex plane as given below:

-2.0177, -0.8793, -0.2120, -0.0912, -0.0517,
-0.0160 + 0.0096i, -0.0160 - 0.0096i, -0.0146, -0.0000

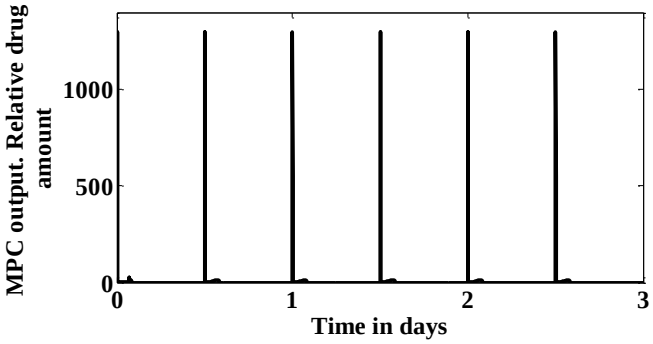

Fig. 9 Bunazosin MPC output.

C. Timolol

Timolol is modeled with nine states and its closed loop model predictive system does not respond to IOP circadian variation as shown in Fig. 10. The set point is selected to be 14 mmHg.

Again the elimination of the circadian pattern can be attributed to the high order and the sub-micro Hertz behavior of the Timolol plant model.

There is a small steady state error in IOP response which is not noticed in the case of Latanoprost or Bunazosin. Fig. 11 shows the Timolol MPC output as it tries to control IOP.

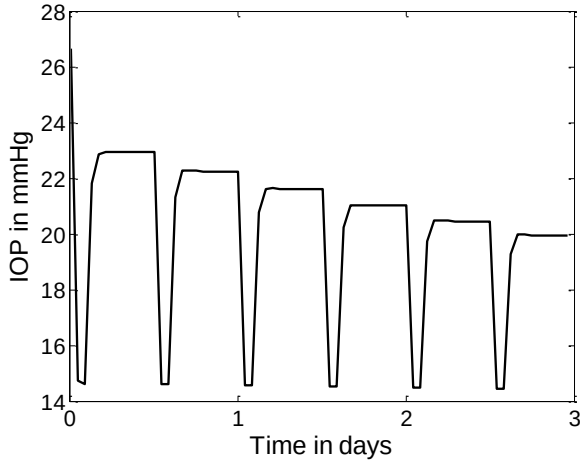

Fig. 10 Timolol IOP response.

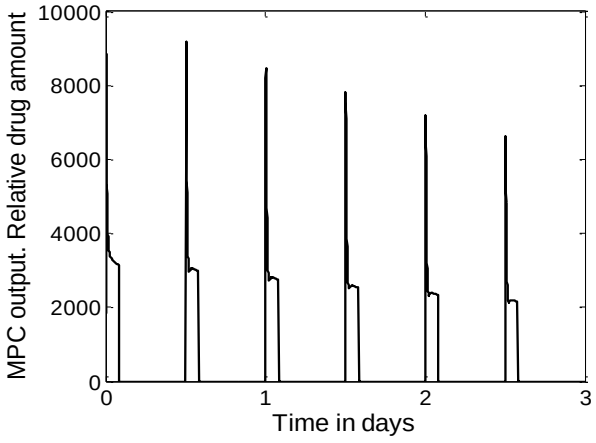

Fig. 11 Timolol MPC output.

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D. PF-04475270

In the same way, PF-04475270 as an ophthalmic drug model with six states was able to eliminate IOP circadian pattern in closed loop simulation, as shown in Fig. 12. The set point is 80% of the initial IOP. The system is stable with no apparent overshoot, undershoot or steady state error, and its MPC output is bounded as shown in Fig. 13.

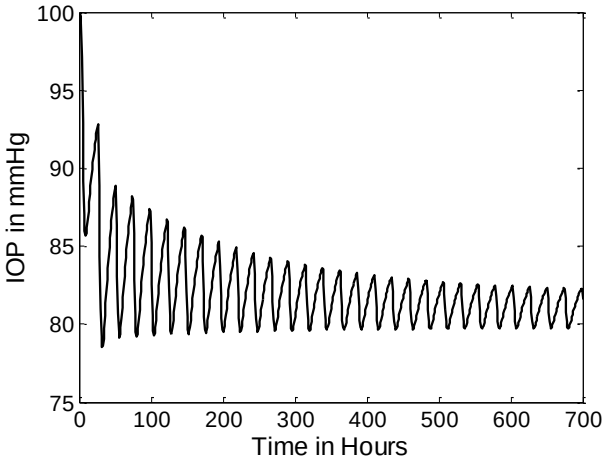

Fig. 12 PF-04475270 IOP response.

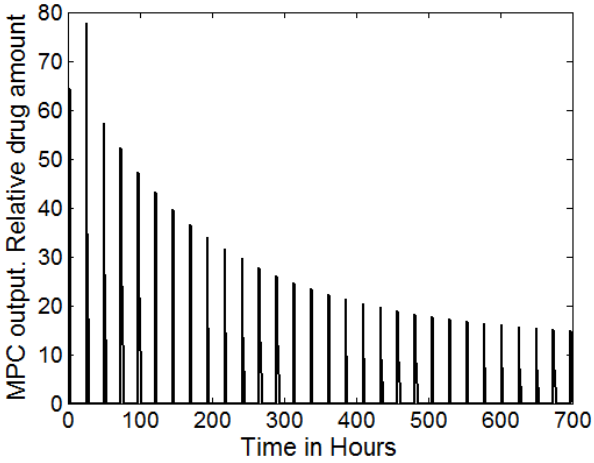

Fig. 13 PF-04475270 IOP MPC response.

Timolol and PF-04475270, also, possess poles on the left hand side of the complex frequency plane [9]. All drugs model predictive systems' controllers are stable and passed the Matlab review tests.

IV. Conclusion

The four drugs model predictive control systems suppress IOP circadian pattern for high modeling orders. The closed loop IOP control systems suggested, are noninvasive and could open a new way of controlling IOP and avoiding IOP glaucoma risk factor. Population-based studies are required for obtaining human representative PKPD models that include time and frequency of dosing functions. The safety and implementation of such systems are proposed as future work, where hydrogels, CLS, and impeded systems can be combined together to realize the automatic non-invasive IOP control systems.

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