Critical Factors for Metformin Osmotic Controlled Release Pump

García-Flores Mirna¹, Melgoza-Contreras Luz María² and Hernández-Baltazar Efrén*¹

¹Facultad de Farmacia Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, C.P. 62209, Cuernavaca Morelos, México.
²Departamento de Sistemas Biológicos Universidad Autónoma Metropolitana, Calzada del Hueso 1100, C.P. 04960, Ciudad de México, México.

Authors’ contributions

This work was carried out in collaboration among all authors. Author GFM made the experimental part and performed the statistical analysis. Author MCLM review the experimental part, the statistical analysis and review the draft of the manuscript. Author HBE managed the project, wrote the first draft and managed the literature searches. All authors read and approved the final manuscript.

ABSTRACT

Aim: Studied the critical factors in the design of an osmotic pump with metformin release rate constant at 4%/hr in diabetes mellitus within 24 hr. with the goal to reduce daily medications.

Study Design: Experimental design 3²

Methodology: In vitro drug release profiles for 24h. The effects of different formulation variables, that is, concentration of hydrophilic polymer, diameter of drug releasing orifice and coating thickness, on the drug release profile were investigated. Also, the impact of pH, osmotic pressure and morphology with stereo microscopy and scanning electronic microscopy of the osmotic pumps were investigated. At last, osmotic pumps surface was analyze with scanning electronic microscopy.

Results: Metformin osmotic pump were successfully prepared in this study to overcome the weak point of multiple doses and great concentration fluctuation of metformin. The formulation determined finally have a release orifice of 700 mm and 3.0% of weight gain, achieved the desired

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*Corresponding author: E-mail: efrenhb@uaem.mx
The effect which can realize the constant drug release rate at the first 24 hr.

**Conclusion:** The developed osmotic systems have a linear release near 4%/hr. and demonstrated that the behavior was independent of the agitation intensity and the pH of the gastrointestinal apparatus.

**Keywords:** Critical factors; elementary osmotic pumps; metformin; diabetes; zero order release.

**1. INTRODUCTION**

Diabetes mellitus occurred in 425 million adults in 2019, and two thirds are of working age [1]. Diabetes is a major public health problem and one of the four non-transmissible diseases (NCDs) selected by world leaders to intervene on a priority order. Diabetes type 2 (is a lifelong disease that keeps the body from using insulin the way it should [2]). Most affected people have type 2 diabetes, which used to be exclusive to adults, but now also occurs in children [3].

Clinical evidence now suggests that most of metformin benefits originate from its actions in the gut, involving hormone signaling by glucagon-like peptide 1 and peptide YY. Growth differentiation factor 15, also mainly produced in the gut, was first identified as a biomarker for metformin use but is now suggested to play a significant role in e.g. weight loss of pre-diabetics.

Metformin is water soluble drug, however, due to the short half-life of the metformin, the tablet has to be administered 2 to 3 times a day, causing inconvenience to patient and fluctuations of plasma concentration [4].

Controlled drug delivery systems for oral applications are widely used clinically. Osmotic systems are a controlled drug delivery device based on the principle of osmosis, which offer many advantages, such as simple method in operation, low dosing frequency, uniform blood concentration, and so on. Drug release from these systems is independent of physiological factors, such as presence or absence of food, pH of the gastrointestinal (GI) tract, and so on. Release behavior follow zero order kinetics [5].

The aim of the present investigation was to prepare an elementary osmotic pump with metformin release rate constant at 4%/hr. within 24 hr. with the goal to reduce daily medications.

**2. MATERIALS AND METHODS**

**2.1 Materials**

The following listed drugs, excipients, and chemicals were purchased from commercial sources and used as received: Metformin HCl (DVA Mexico from Wanbury Lot MT00160112), Methyl cellulose A15 (Dow Wolf Cellulosics), cellulose acetate (CA-320S Eastman), ethylcellulose (Aquacoat FMC Biopolymer), dibutylsebacate (Sigma-Aldrich), magnesium stearate, sodium croscarmellose, propyleneglycol, acetone, solvents of reagent grade and deionized water were used in all the experiments.

**2.2 Preparation of the Elementary Osmotic Pump of Metformin**

The core tablets of metformin were prepared by direct compression and 30 tablets were made in hydraulic press with manometer (Perkin Elmer) at 20 kg/cm², 10.0 mm round standard concave punches.

Experimental design $3^2$ with factor 1 lubricant (magnesium stearate) and levels 0, 0.25 and 0.5%, factor 2 diluent (methylcellulose) amount and levels 0.0, 100 and 200 mg. Metformin was constant 500 mg, NaCl 100 mg. The response variables were hardness, friability and disintegration time. The core tablets were evaluated for hardness, friability, thickness, weight variation and disintegration time. The hardness and friability of the tablets were determined by Schleuninger Pharmatron model 6D hardness tester and tablet friabilator tester, Vernier caliper, Ohaus balance and tablet disintegration tester, respectively. After these, the results were used to select the appropriate formulation.

**2.3 Optimization of the Cores**

Following the first experimental design, the best formulation was selected, the release profile of the press-coated tablet exhibited a period without drug release (time lag). Consequently a constant rate and complete the release phase, [6] but the lag time in the osmotic systems is a main worry for these release systems, so we make four batches with different amount of disintegrants (3.0, 4.0, 5.4 and 6.5 %). Coded NO1 (3.0%), NO2 (4.0%), NO3 (5.4%), and NO4 (6.5%). Then, we started with the coating.
2.4 Coating of Osmotic Cores

The core tablets of metformin were coated in a stainless-steel pan with a coating solution whose composition is given in Table 1. The coating solution was prepared by adding various components to the solvent mixture in a sequential manner. Each component added was allowed to dissolve before the next component was added. The coating conditions were set as follows: stainless-steel pan, 300 mm diameter; without baffles; rotation rate of the pan, 30 rpm; nozzle diameter of spray gun, 1 mm; spray rate, 8–10 mL/min; spray pressure, 25 psi; and drying temperature, 35°C. Coating was continued until desired target weight gain was obtained on the cores (3.0 and 6.0 %). Thereafter, in all cases, metformin cores coated were stored prior to evaluations. Coating formulations are showed in Table 1.

Next, a drug release orifice with the size of 350 μm and 700 μm was drilled into one side of coated cores center using a standard needle. For the study, the effect of the orifice diameter, polymer type (cellulose acetate and ethyl cellulose), thickness of the coating (3.0 and 6.0%) and release mechanism (porous system or orifice diffusion) were evaluated Table 2.

2.5. In Vitro Dissolution and Analysis

In vitro drug release of the formulations was carried out in a dissolution apparatus with a basket setting (Varian VK 7010). Operating conditions were 37± 0.5°C, and a basket speed of 100 rpm with 900 mL of different pH mediums selected for the study. The samples were withdrawn (3.0 mL) at different time intervals (0.5, 1, 2, 4, 6, 8, 10, 12 y 24 hours) and replaced with an equivalent amount of fresh medium. The dissolution samples were analysed using a validated UV-Vis method at 220 nm for pH 1.2 or 233 nm for pH 6.8 and 7.4. After analyzing the drug content in the dissolution samples, corrections were made for the volume replacement, and a graph of cumulative percentage of drug release versus time was plotted.

2.6 Surface Morphology Study of Coating Membrane

The morphology of coating film was studied before and after drug release experiments by stereoscopic microscope at 8 an 66X and scanning electron microscopy (SEM-JSM 5610). The tablets were dried overnight at 40°C before SEM analysis. The samples were mounted on double coated conductive carbon tape. Then, samples were coated with gold and scanned at an accelerating voltage of 15 kV with magnification ranging from 50 to 550X and spatial resolution ranging from 20 to 100 μm. [7].

Table 1. Coating formulations for metformin HCl core formulations

| Ingredient          | Semipermeable | Porous   |
|---------------------|---------------|----------|
| Cellulose acetate   | 4.0           | Ethyl cellulose | 3.0   |
| Propylenglycol      | 1.0           | Dibutyl sebacate | 0.75  |
| Red color           | 0.05          | HPMC      | 1.5   |
|                     |               | Blue color | 0.05  |
| Total solids %      | 5.05          |           | 5.30  |

Table 2. Final codification for the osmotic systems with, different orifice, different coating polymer, and different polymer

| Osmotic core | Coating polymer | Weight gain (%) | Orifice diameter (μm) | Code             |
|--------------|-----------------|-----------------|-----------------------|------------------|
| NO2          | AC              | 3               | 700                   | NO2-AC-3/700     |
| NO4          | AC              | 3               | 700 without orifice   | NO4-AC-3/700     |
|              |                 | 3               | 350                   | NO4-AC-3/350     |
|              |                 | 6               | 350 without orifice   | NO4-AC-6/350     |
|              |                 | 6               | 700 without orifice   | NO4-AC-6/700     |
| EC           | 3               | 700 without orifice | NO4-EC-3/700     |
|              |                 |                 |                       | NO4-EC-3/3/SO   |
3. RESULTS

3.1 Experimental Design

As a first step, the osmotic cores needs to have good mechanical properties, so the selection of the composition of the cores was based on the best results in hardness, friability and disintegration time. The summary result and the best value result of uniform design are shown in Table 3. The batch 9 have the better results, so the study was continued with this formulation.

This selection was confirmed with the results from the Pareto graphics from the dependent factors. Fig. 1.

3.2 Formulation Optimization

After the four experiments the concentration of disintegrant selected was 4.0%. For comparison, the concentration 6.5% was selected for ethylcellulose coating. The results are shown in Table 4.

3.3 Release Models and Kinetics

From Fig. 2, it was possible to discuss the effect of the release mechanism and the lag time of the systems.

In order to describe the kinetics of drug release from the preparations, various mathematical equations have been proposed. The zero-order equation (Eq. 1), the first-order equation (Eq. 2), the Higuchi model (Eq. 3) and the Hixson–Crowell model (Eq. 4) were used in the present study:

\[ Q_t = K_0 t \]  
(1)

\[ \ln Q_t = \ln Q_0 - K_1 t \]  
(2)

\[ Q_t = K_H t^{1/2} \]  
(3)

\[ Q_0^{1/3} - Q_t^{1/3} = K_H C t \]  
(4)

Where \( Q_t \) is the amount of drug released in time, \( t \), \( Q_0 \) is the initial amount of drug in the osmotic core, \( K_0, K_1, K_H \) y \( K_H C \) are the rate constants of the order zero, first order, Higuchi and Hixson–Crowell models respectively.

Drug release data of the optimized formulation were fitted to various mathematical models (Zero-order, First-order, Higuchi and Hixson–Crowell) to check the kinetics of drug release. The correlation coefficient (r) was used as criteria for choosing the most appropriate model [8] (Table 5). The value of r for zero-order release model was found to be 0.9987; which was highest amongst all the kinetic models applied. In the case of samples with thin osmotic membranes, the best fit model was Higuchi, because the osmotic pressure in the system equals the pressure in the dissolution medium.

In order to measure the impact of the release orifice and thickness of the coating membrane, we made a comparison with similarity values. Fig. 3 and Table 6.
Table 3. Experimental design for full $3^2$ factorial design

| Lote | MC (mg) | % EstMg | Hardness (Kp) | Friability (%) | T Desint. (min) |
|------|---------|---------|---------------|----------------|----------------|
| 1    | 0       | 0       | 6.5           | 25             | 0.08           |
| 2    | 100     | 0       | 10.1          | 3.8            | 10.33          |
| 3    | 200     | 0       | 14            | 2.2            | 12.13          |
| 4    | 0       | 0.25    | 7.5           | 8.3            | 0.25           |
| 5    | 100     | 0.25    | 11.2          | 2.5            | 8.0            |
| 6    | 200     | 0.25    | 19.6          | 1.64           | 14.33          |
| 7    | 0       | 0.5     | 6.1           | 8.5            | 0.37           |
| 8    | 100     | 0.5     | 11.8          | 3.2            | 7.58           |
| 9    | 200     | 0.5     | 20            | 1.56           | 13.67          |

The similarity of release profiles was evaluated by similarity factor ($f_2$) recommended by FDA. The $f_2$ value was calculated by the following equation [9].

$$f_2 = 50 \times \log \left[ 1 + \frac{1}{2} \sum_{n}^{m} (R_i - T_j)^2 \right]^{-0.5} \times 100$$  \hspace{1cm} (5)

This method is more adequate to compare dissolution profile when more than three or four dissolution time points are available and can only be applied if the average difference between $R_j$ and $T_j$ is <100. The FDA and EMEA suggested that two dissolution profiles were declared similar if $f_2$ was between 50 and 100 [10]. On the contrary, they were dissimilar if $f_2$ was between 0 and 50. Values for similarity factor between different orifice diameter showed that the impact of the release orifice diameter was insignificant. On the other hand, values for similarity factor between thickness of the coating membrane under the base of weight gain showed that the thickness was significant because the values were lower than 50.

In Fig. 4, it was possible to discuss the impact of the orifice and the comparison between the kind of polymer coating (AC and EC).

3.4 Drug Release as a Function of Agitation Intensity

To study the effect of agitation intensity on drug release, in vitro drug release studies were done at two different rotational speeds for optimized formulation at relatively high (100 rpm), and low (50 rpm) using USP-I (basket) type dissolution apparatus and three different pHs 1.2, 6.8 and 7.4. Results obtained were compared using similarity factors $f_2$ values as shown in Table 7.

Table 4. Composition of the final osmotic cores and mechanical properties

| Component | NO2 | NO4 |
|-----------|-----|-----|
| Metformin | 58.8| 58.8|
| NaCl      | 11.7| 11.7|
| Mg. Stearate | 0.5 | 0.5 |
| Methylcellulose | 24.9 | 22.35 |
| Crosscarmellose | 4  | 6.55 |
| Hardness (Kp) | 11.1 | 11.2 |
| Friability (%)  | 0.097 | 0.30 |
| Disintegration time (min) | 9.85 | 2.94 |

3.5 Influence of NaCl Concentration in Dissolution Medium on Drug Release

The influence of the NaCl concentration in dissolution medium on in vitro drug release was also studied. These results are showed in Fig. 5. Drug release decreased over the concentration of NaCl. It was because, the addition of NaCl could reduce the concentration gradient between the osmotic system and the dissolution medium.

Table 5. Fitting of drug release data from optimized formulation with some mathematical models

| MODEL               | NO2-AC-3/700 | NO4-AC-3/700 |
|---------------------|--------------|--------------|
|                     | m  | b  | r   | m   | b  | r   |
| ZERO ORDER (%/h)    | 3.8 | 1.93 | 0.9774 | 3.6 | -3.42 | 0.9987 |
| FIRST ORDER (h⁻¹)   | -0.09 | 4.55 | -0.9877 | -0.061 | 4.48 | -0.9856 |
| HIGUCHI (½h⁻¹)      | 21.46 | -21.71 | 0.9888 | 19.28 | -23.51 | 0.9659 |
| HIXSON-CROWELL (¼h⁻¹)| -0.15 | 2.84 | -0.8714 | -0.167 | 3.28 | -0.8992 |
Fig. 2. *In vitro* dissolution profiles of the metformin with different amount of disintegrant

Fig. 3. Comparing the dissolution profiles with the impact of the size of the release orifice and thickness of the coating
Table 6. Comparison between release orifice and membrane thickness

| Weight gain/orifice diameter | 350 μm | 700 μm |
|-----------------------------|--------|--------|
|                            | 3%     | 6%     |
| m                           | 3.54   | 2.05   |
| b                           | 1x10^{-15} | 3x10^{-15} |
| r                           | 0.9966 | 0.9885 |
| t_{lag}                     | 0.89   | 2.11   |

3% Weight gain/orifice diameter

\[ f_2 = 89.5 \]
\[ P = 0.896 \]

6% Weight gain/orifice diameter

\[ f_2 = 93.3 \]
\[ P = 0.120 \]

\[ f_2 = 31.76 \]
\[ P << 0.05 \]

Fig. 4. Effect of the size of the release orifice and the kind of polymer

3.6 Investigation of Drug Release Mechanism

There are three mechanisms that contribute to the release of active material from controlled porosity osmotic pump i.e., drug release driven by the mechanism of osmotic pressure, size and number of pores formed in the membrane and water uptake of the membrane. To demonstrate the role of osmotic pressure for drug release, the optimized formulation of controlled porosity osmotic pump was subjected to in vitro drug release study in different concentrations of NaCl (0.5, 1 and 2 mol/l) used as dissolution medium [11].

3.7 Physical Observation and Surface Morphology before and after Drug Release Study

Physical change in the dimension of the tablet was observed before and after drug release study. The shape of the tablet changed to oval, which was filled with liquid inside. We first used stereoscopic microscopy at 8X and 66X to measure the release orifice in Fig. 6.

The SEM photographs showed the semipermeable membrane was intact after completion of drug release study. The
morphological changes in semipermeable membrane are shown by SEM images.

Physical Observation of elementary osmotic pumps (EOP).

To confirm physical integrity of the coated semipermeable membrane, physical changes in dimensions of EOP were observed carefully after drug release study. The diameter of the tablet was measured before and after the drug release study as shown in Figs. 6 and 7.

![Fig. 5. Release profiles at different molarity in the dissolution medium](image1)

![Fig. 6. Drilled the release orifice and the morphological changes during the release](image2)
Table 7. Comparison the release profiles at different rotational speed and different pH

| Stirring rate | 100 rpm | 50 rpm |
|---------------|---------|--------|
| pH            |         |        |
| m (klib)      | 3.43    | 3.54   | 3.60   | 3.36   |
| r             | 0.9877  | 0.9966 | 0.9974 | 0.9975 |
| t_lag         | 2.0     | 0.9    | 1.2    | 1.4    |
| Factor f_2    | 1.2/6.8 = 65 | 6.8/7.4 = 52 |
|               | 1.2/7.4 = 59 | 100/50 = 78.4 |

Fig. 7. Stereoscopic microscopy: The release orifice of 350 μm and 700 μm were observed at 8X and 66X

In Fig. 8, the gold coating of the osmotic cores and the cut point at the release orifice are shown.

In Fig. 9, the osmotic core before the release of metformin, and the thickness of the coating film are shown.

In Fig. 10, the coating film after the release at different magnifications is shown. Notice that all materials went out of the system.

4. DISCUSSIONS

Controlled release formulations of metformin were developed based on osmotic technology. The effect of different formulation variables were evaluated in an experimental design 32 to study the impact of the diluent and the lubricant. These factors were chosen because the diluent has very good hydrophilic properties, while the lubricant has lipophilic properties which normally in tablets have negative effect over the hardness and friability. The mechanical properties like hardness, friability and disintegration time ensure that the core avoids crushing during the coating process.

The process of optimization of the osmotic pumps implies: The selection and confirmation of
the type and range of factors and optimization parameters to be evaluated for the target release profile are critical. In order to control the lag time of the osmotic system, we tested 4 concentrations of the disintegrant agent in order to reduce the lag time to maximum possible. The lag time probably is one of the most important factors in osmotic systems because, this time defines when the systems start to release the drug. The pumping drug rate from the core have been expressed as: [12]

\[
\frac{dm}{dt} = \frac{AK\pi C}{h}
\] (6)

This fundamental equation is applicable to all osmotically driven pumps as well as controlled porosity osmotic pump tablets [13]. But, all these systems present lag time, so the equation needs to add a constant. This constant will be independent of the diffusion of the drug, but dependent on the permeation of the water into the osmotic systems and the capacity of the membrane to swell and allow the entrance of the water to start the osmotic process.

Fig. 8. The gold mounting of the osmotic systems and micrograph at 110X of the release orifice

Fig. 9. Transversal view of the osmotic system at 35X and the thickness of the osmotic coating at 500X
In our results, the use of different concentrations of disintegrant agent not showed differences over the lag time of the systems, as seen in the Fig. 2.

The release profiles showed that the systems released the metformin in a zero order kinetics, demonstrating that the osmotic systems release was independent of the rotational speed and pH of the medium. The results with the two different orifices showed that the orifice with 700 μm were the better option to reach the goal of the project, near 4%/h.

On the other hand, osmotic systems coating with AC and release orifice of 700 μm has 4 times better release than the osmotic systems coating with EC, whether the EC systems have orifice or not.

The typical orifice size in osmotic pumps ranges from 600μm to 1 mm [14]. These study showed that the size of the release orifice of 700 μm showed better release, while the other release orifice or without orifice showed lower release.

The presence of salts in the dissolution medium was an important factor because, it reduced the release until 10 times and this behavior was lineal.

Finally, the result of microscopic study showed that the osmotic membrane remains until all the release experiments and the thickness of the osmotic coating was about 100 nm.

5. CONCLUSION
Metformin osmotic pump tablets were successfully prepared in this study to overcome the weak point of multiple doses and great concentration fluctuation of metformin.

The formulation determined finally had a release orifice of 700 μm and 3.0% of weight gain, achieved the desired effect which can realize the constant drug release rate at the first 24 h.

The developed osmotic systems had a linear release near 4%/h. and demonstrated that the behavior was independent of the agitation intensity and the pH of the gastrointestinal apparatus.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES
1. IDF. Atlas de la diabetes de la FDI [Internet]. Brussels: Pfiser, MSD, Alliance. 2019;1-2 . [Cited 2020 Sep 05] Available:https://www.diabetesatlas.org/upload/resources/material/20200302_133352_2406-IDF-ATLAS-SPAN-BOOK.pdf
2. WebMD [Internet]. [Cited 2020 Sep 05] Available:https://www.webmd.com/diabetes/type-2-diabetes
3. OMS. Informe mundial sobre diabetes. 2016;16(3):1-4. Available:www.who.int/diabetes/global-report. WHO/NMH/NVI/
4. Qin C, He W, Zhu C, Wu M, Jin Z, Zhang Q, et al. Controlled release of metformin hydrochloride and repaglinide from sandwiched osmotic pump tablet. Int J Pharm [Internet]. 2014;466(1-2):276-85. [Cited 2020 Sep 05]
   Available:https://pubmed.ncbi.nlm.nih.gov/24607209/
   DOI: 10.1016/j.ijpharm.2014.03.002
5. Qun-Li Song, Ping Li & Yu-Min Li. A novel solubility-modulated granules through porosity osmotic pump for controlled carvedilol delivery. Pharm. Dev. and Tech [Internet]. 2011;17(6):666-676. [Cited 2020 Sep 05]
   Available:https://pubmed.ncbi.nlm.nih.gov/21486184/
   DOI:10.3109/10837450.2011.565348
6. Shan-Yang Lin, Mei-Jane Li, Kung-Hsu Lin. Hydrophilic excipients modulate the time lag of time-controlled disintegrating press-coated tablets. AAPS PharmSciTech 5 [Internet]. 2004;5:25-29. [Cited 2020 Sep 05]
   Available:https://link.springer.com/article/10.1208/pt050454
   DOI:10.1208/pt050454
7. Idem reference 5.
8. Wen-Jin Xu, Ning Li, Chong-kai Gao, Preparation of controlled porosity osmotic pump tablets for salvianolic acid and optimization of the formulation using an artificial neural network method. Acta Pharm. Sinica B [Internet]. 2011;1(1):64–70. [Cited 2020 Sep 05]
   Available:https://www.sciencedirect.com/science/article/pii/S2211383511000037
   DOI: 10.1016/j.apsb.2011.04.002
9. Yuenan Li, Hao Pan, Hongliang Duan, Jianting Chen, Zhihong Zhu, Jingxin Fan, Et Al. Double-layered osmotic pump controlled release tablets of actarit: In vitro and in vivo evaluation. Asian J. of Pharm. Sci. 14 [Internet]. 2018;14(3):340–348. [ Cited 2020 Sep 05]
   Available:https://www.sciencedirect.com/science/article/pii/S1818087617308504
   DOI: 10.1016/j.ajps.2018.05.009
10. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. J Control Release [Internet]. 2000; 68(2): 145-56. [Cited 2020 Sep 05].
   Available:https://pubmed.ncbi.nlm.nih.gov/10925123/
   DOI: 10.1016/s0168-3659(00)00243-1
11. Thakkar HP, Pancholi N, Patel CV. Development and evaluation of a once-daily controlled porosity osmotic pump of tapentadol hydrochloride. AAPS PharmSciTech [Internet]. 2016; 17(5): 1248-60. [Cited 2020 Sep 05]
   Available:https://pubmed.ncbi.nlm.nih.gov/26677859/
   DOI: 10.1208/s12249-015-0463-1.
   Epub 2015 Dec 17. PMID: 26677859.
12. Chinmaya Keshari Sahoo, Nalini Kanta Sahoo, Surepalli Ram Mohan Rao, Muvvala Sudhakar, Kokkula Satyanarayana. A review on controlled porosity osmotic pump tablets and its evaluation. Bulletin of Faculty of Pharmacy [Internet]. 2015;53(2):195–205. [Cited 2020 Sep 05]
   Available:https://www.sciencedirect.com/science/article/pii/S1110093115000319
   DOI: 10.1016/j.bfopcu.2015.10.004
13. Sahoo CK, Rao SRM, Sudhakar M, Sahoo NK. Advances in osmotic drug delivery system. J Chem Pharm Res [Internet]. 2015;7(7):252–73. [Cited 2020 Sep 05]
   Available:https://www.jocpr.com/articles/advances-in-osmotic-drug-delivery-system.pdf
14. Singh K, Walia M, Agarwal G, Harikumar S. Osmotic pump drug delivery system: A novel approach. JDDT [Internet]. 2013; 3(5):156-62. [cited 2020 Sep 05]
   Available:http://jddtonline.info/index.php/jddt/article/view/636
   DOI: 10.22270/jddt.v3i5.636

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