International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

CONTROLLED POROSITY OSMOTIC PUMP: A REVIEW

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ABSTRACT

An oral route remains the most favored route for administration of drugs. Despite of many dosage forms that are administered via oral route, the Controlled Porosity Osmotic Pump (CPOP) has its own stand. CPOP is based on principal of osmosis, which provides better release of a drug that independent on pH and agitation intensity. The CPOP being an easy to formulate as compare to other oral osmotic drug delivery such as Elementary osmotic pump, hence creates opportunity for many manufacturers. The points lime lighted in this paper are the historical development, formulation factors, the research carried out, and patents. In present paper, the CPOP is reviewed till date.

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Key words: *Controlled Porosity Osmotic Pump, Oral Osmotic Drug Delivery System, Elementary Osmotic Pump, Osmosis.*

INRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. [1] Conventional oral drug delivery system has little control over their release which is unpredictable. Frequent dosing is needed to achieve the therapeutic level but this can cause the side effect. But from last three decades there is huge development in oral drug delivery system. The drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. [2] In the group of Control drug delivery system (CDDS) the release of drug molecule from the drug delivery system is activated by some physical, chemical, or biochemical processes. The classification of control drug delivery system is described in figure1. [3] After the first report of an osmotic effect by Abbenollet (1748) and Pfeffer obtained the first quantitative measurement (1877) there was implementation of osmosis in different field had started. Also controlled drug delivery system was developed on the basis of osmosis. Historical aspect of osmotic drug delivery system mentioned in table 1. [4]

Table 1- Development of Osmotic drug delivery system.

Year	Historical aspect of osmotic drug delivery system
1748	First report of osmosis
1877	Quantitative measurement of osmotic pressure
1955	First osmotic pump by Rose-Nelson developed pump for pharmaceutical research
1973	Higuchi- Leeper introduced a new version of Rose-Nelson pump with certain modification
1973	Osmoticaly powdered agent dispense device with filling means.
1975	Introduced the first oral osmotic pump i.e. EOP. It was the major the major mile stone in the field of oral osmotic drug delivery system.
1976	Patent granted on the design of Alzet osmotic pumps which later extensively used as an experimental research tool in laboratory animal.
1979	Osmotic bursting drug delivery device
1982	Patent issue for an osmotic system which consist of a layer of a fluid swell able hydro gel to deliver insoluble to very insoluble to very insoluble drug.
1984	First report of combination therapy by use of push pull osmotic pump.
1985	Controlled porous osmotic pump was developed from which drug is leached out from the coating, eliminating the need of complicated laser drill procedure.
1986	Patent issue claiming a delivery system for controlled administration of drug to ruminants.
1989	Developed of Push Pull osmotic pump of Nefedipine (Procardia XL) by Pfizer which was the largest selling cardiovascular product in US market until 1995
1995	Patent to an osmotic dosage form for liquid drug delivery .The system consist of an outside semi permeable wall, middle osmotic active layer, capsule containing an active agent and an orifice for delivery of the agent.
1999	Asymmetric membrane capsule is introduced to deliver the drug through the osmotic pressure.
2000	DUROS Leurpolid implants i.e. Viadur approved as first implantable osmotic pump for human by US FDA.
2001	Patent granted for dosage form comprising liquid drug formulation that can self emulsify to enhance the solubility, dissolution, & bioavailability of drug.
2003	First report osmotic floating system.

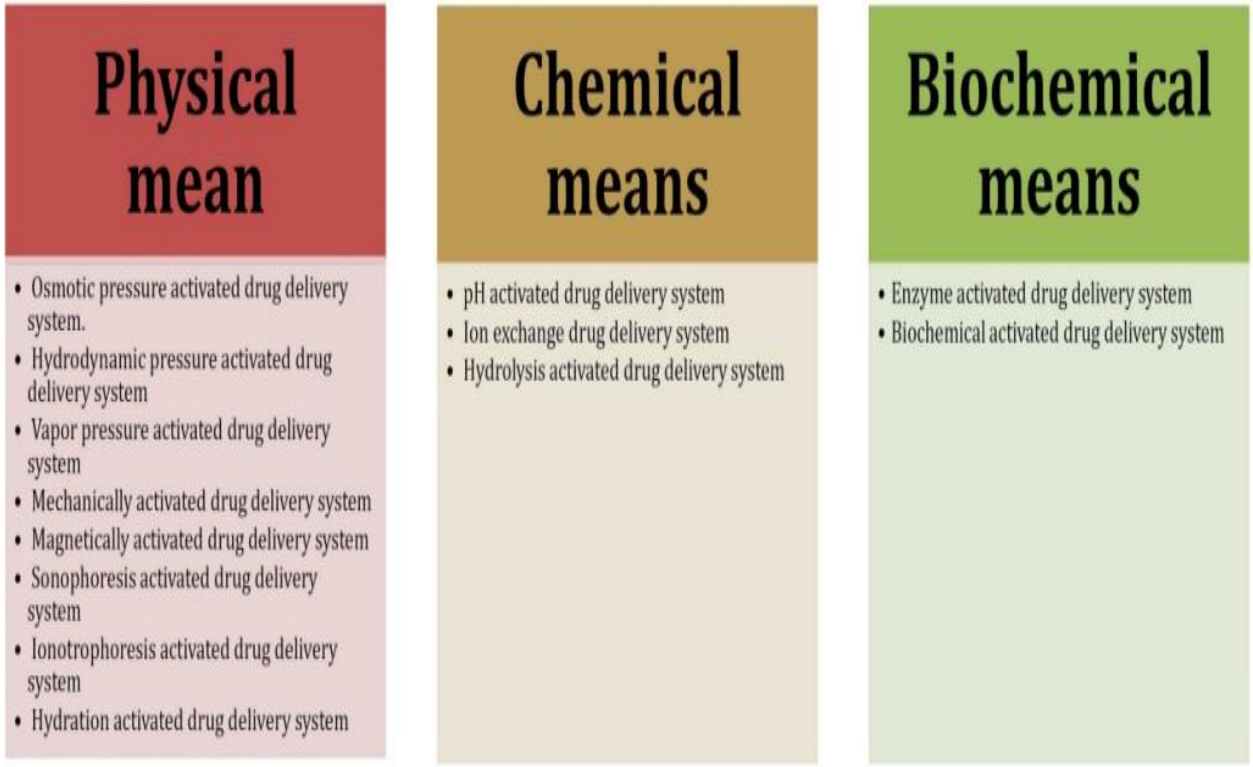


Figure 1: Classification of Control drug delivery system

2. The Phenomenon of Osmosis:

As Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. [5]

2.1 Principles of Osmosis

The first report of an osmotic effect dates to Abbenollet (1748). But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = \Phi\ c\ r\ t$$

Where Φ is the osmotic coefficient of the solution, c is the molar concentration of sugar in the solution, r is the gas constant, t is the absolute temperature.

Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 8 atm for Adipic acid up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through a membrane is given by the equation,

$$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L$$

Where dv\dt is water flow across the membrane of area A, thickness L, and the permeability Q in cm2, Δ π is the osmotic pressure difference between the two solutions on either side of the membrane. This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.[6]

3. Classification of Osmotic Drug Delivery System:

A. Implantable

I. The Rose and Nelson Pump
II. Higuchi Leeper Pump
III. Higuchi Theuwes pump
IV. Implantable Miniosmotic pump

B. Oral osmotic Pump

I. Single chamber osmotic pump: Elementary osmotic pump
II. Multi chamber osmotic pump: Push pull osmotic pump, Osmotic pump with non expanding second chamber
III. Specific types: Controlled porosity osmotic pump, Osmotic bursting osmotic pump, Liquid OROS, Delayed Delivery Osmotic device, Telescopic capsule, OROS CT (colon targeting), sandwiched oral therapeutic system, Osmotic pump for insoluble drugs, Monolithic osmotic system and OSMAT.

4. Controlled porosity osmotic pump

The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner et al.[7] The controlled-porosity osmotic pump tablet is a spray-coated or coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semipermeable wall in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pore screened by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after water is imbibed across the semipermeable membrane. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media.

4.1 Advantages

A. The controlled porosity osmotic pump can be following zero order kinetics and thus better control over the drug's in vivo performance is possible.
B. The drug release is independent of the gastric pH and hydrodynamic conditions.
C. The delivery rate of drug from these systems is highly predictable and can be programmed by modulating the terms.
D. Drug release from the controlled porosity osmotic pump exhibits significant in vitro-in vivo correlation [IVIVC] within specific limits.
E. No need of drilling.
F. The rationale for this approach is that the presence of water in GIT is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
G. Production scale-up is easy [8, 9, 10].

4.2 Disadvantages

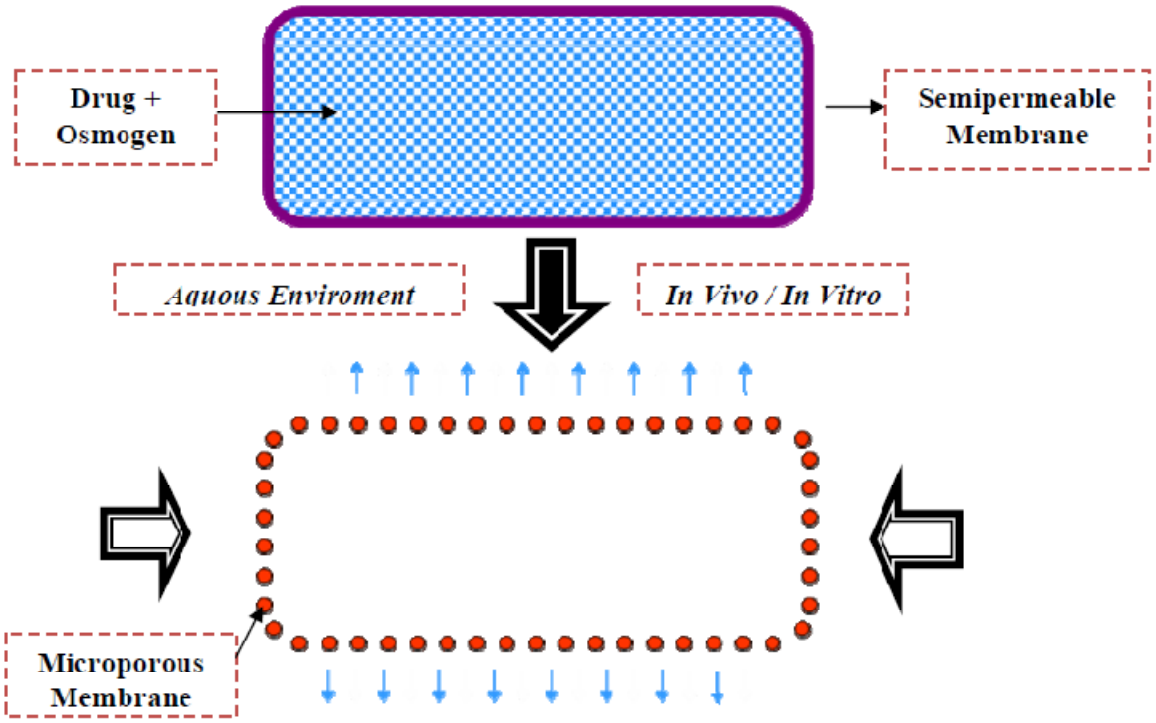
A. Retrieval of therapy is not possible in the case of unexpected adverse events.
B. Drug release from the osmotic systems is affected to some extent by the presence of food.
C. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping [8, 9, 10].

4.3 Drug release mechanism

As shown in figure 2, when controlled porosity osmotic pump is in aqueous environment the water soluble channeling agent get dissolve and forms a pore in coat. The water enters through semipermeable membrane and forms a solution of drug which get release through pores. Rate of water inlet is depending on type and concentration of osmotic agent and the drug release is depend on hydrostatic pressure created by inlet water and size and number of pores.**4.4 Basic component of controlled porosity osmotic pump4.4.1 Drug:** Basic criteria for selection of drug

i. It should have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems.
ii. It should be water soluble.
iii. It should be potent.

Figure 2: Drug release mechanism of controlled porosity osmotic pump.



4.4.2 Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Compounds that can be used as osmagents are shown in table 2 and some osmotic agent with their osmotic pressure shown in table 3, [11]

Table 2- Compounds that can be used as Osmagents

Category	Examples
Water-soluble salts of inorganic acids	Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate, etc.
Water soluble salts of organic acids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
Carbohydrates	Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc.
Water soluble amino acids	Glycine, leucine, alanine, methionine, etc.
Organic polymeric osmogents	Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, polyacrylamides, etc.

Table 3- Some osmotic agent with their osmotic pressure

Sr. No	Compound/ mixture	Osmotic Pressure (atm)	Sr. No	Compound/ mixture	Osmotic Pressure (atm)
1	Adipic acid	8	16	Melanic acid	117
2	Fumaric acid	10	17	Mannitol - Lactose	130
3	Lactose	23	18	Sucrose	150
4	Sodium phosphate monobasic,H_2O	28	19	Mannitol - Sucrose	170
5	Sodium phosphate Dibasic,$12H_2O$	31	20	Dextrose – Sucrose	190
6	Sodium phosphate dibasic, $7H_2O$	31	21	Mannitol – Dextrose	225
7	Sodium phosphate tribasic, $12H_2O$	36	22	Lactose – Dextrose	225
8	Mannitol	38	23	Potassium chloride	245
9	Potassium sulphate	39	24	Lactose - sucrose	250
10	Tartaric acid	67	25	Fructose	355
11	Citric acid	69	26	Sodium chloride	356
12	Dextrose	82	27	Mannitol – Fructose	415
13	Sorbitol	84	28	Sucrose – Fructose	430
14	Xylitol	104	29	Dextrose – Fructose	450
15	Potassium phosphate	105	30	Lactose – Fructose	500

4.4.3 Semipermeable membrane

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. e.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits. Some other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly (vinylmethyl) ether copolymers, poly (orthoesters), poly acetals, poly (glycolic acid) and poly (lactic acid) derivatives.

4.4.3.1Ideal properties of semipermeable membrane

1. It should be stable to both outside and inside environments of the device.
2. It must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device.
3. It should be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane.
4. The membrane must be biocompatible.
5. The material must possess sufficient wet strength (10-5 Psi) and wet modules so (10-5 Psi) as to retain its dimensional integrity during the operational lifetime of the device.
6. The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
7. The reflection coefficient or "leakiness" of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.[12, 13.]

4.4.4 Channeling agents or pore forming agents

These are the water-soluble components which play an important role in the controlled drug delivery systems. When the dissolution medium comes into contact with the semipermeable membrane it dissolves the channeling agent and forms pores on the semipermeable barrier. Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis. Example of pore forming agent- sodium chloride, sodium bromide, potassium chloride, calcium chloride calcium nitrate, glucose, fructose,

mannose, Diethylphthalate, Dibutylphthalate, Dibutylsebacate etc.

4.5 Factors affecting the release of drug through controlled porosity osmotic pump

4.5.1 Drug: Osmotic agent ratio

As concentration of osmotic agent in the tablet core has increases the rate of drug release is also increases. It is due to the increase in osmotic pressure on increasing the concentration of osmotic agent. As different osmotic agent posses the different osmotic pressure the release of drug trough drug delivery system is depend on the type of osmotic agent.

4.5.2 Level of coating thickness

Drug release from the system is inversely proportional to the level of coating thickness. As thickness of coating increases the drug release get decreases.

4.5.3 Porosity of coating membrane

As porosity of coating membrane get increases the rate of drug release is increases. The porosity of coating membrane is depend on the type and concentration of channeling agent.

4.6 Specification of controlled porosity osmotic pump

Specifications of controlled porosity osmotic pump are described in table 4[14].

Table 4- Specification of Controlled Porosity Osmotic Pump

Subject	Specification
Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material
Surfactants	0 to 40, preferably 0.001to 40 parts per 100 parts of wall material
Wall thickness	1 to 1000, preferably 20 to 500 m
Microporous nature Pore forming additives	5 to 95% pores between 10a to 100 m diameter 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer
Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals)
Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass solubility, S, to the core mass density, that is S/, must be 0.1 or lower. Typically it occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

4.8 Research on controlled porosity osmotic pump

Different researchers had made study on different factors in related with CPOP that are mention in table 5. [15-26]

4.9 Recent patent on controlled porosity osmotic pump:

Recent patent on controlled porosity osmotic pump are summarized in table 6.[27]

4.10 Marketed formulation of controlled porosity osmotic pump

Marketed formulation of controlled porosity osmotic pump are enlisted in table 7.

Table 5- Research on Controlled Porosity Osmotic Pump.

Author	Drug	Osmotic agent	Semipermiable membrane	Channeling agent
Pritam *et. al.*	Venlafaxine-Hydrochloride	Sodium chloride	Cellulose acetate	PEG-400 and HPMC K4M

Chong-kai Gao et al	Salvianolic acid	Sodium chloride	Cellulose acetate	PEG-400 and Diethyphthalate
Patel Parth et al	Propranolol Hydrochloride	Sodium chloride	Cellulose acetate	PEG-400
Harnish Patel et al	Glimepiride	Sodium chloride	Cellulose acetate	PEG-400
Rajagopal Kumaravelrajan	Nifedipine and Metoprolol	Dicalcium phosphate	Cellulose acetate	PEG-400 PVP HPMC
B.Prakash Rao et al	Theophylline	Potasium chloride	Ethyl Cellulose	PEG 400 Triacetin Sorbitol Plasdone
Ambikanandan Misra et al.	Oxybutynin chloride	Mannitol	Cellulose acetate	PEG 400 Sorbitol
Basant A. Habib et al.	trimetazidine dihydrochloride	Lactose	Ethyl Cellulose	PEG-400
Mangukia Dhruv k et al.	Glipizide	Mannitol-sucrose Mannitol-Fructose Lactose-Sucrose	Cellulose acetate	Potasium chloride
Mahalaxmi.R et al.	Glipizide	Mannitol	Cellulose acetate	Sorbitol
Zhi-Rong Zhang et al.	sodium ferulate	Sodium chloride	Cellulose acetate	PEG-400
Pradeep R. Vavia et al.	pseudoephedrine	$NaHCO_3$	Cellulose acetate	Diethylphthalate Dibutylphthalate Dibutylsebacate

Table 6- Recent patent on Controlled Porosity Osmotic Pump

Title, Inventors, Year	**Patent No.**
Controlled porosity osmotic pump. John *et al*.1989	ZA198807010
Controlled porosity osmotic pump. John *et al*.1989.	US4880631
Controlled porosity osmotic pump. Himmelstein *et al*.1990.	CA1266827A
Controlled porosity osmotic pump. Zentner *et al*.1990.	US4968507
Controlled porosity osmotic pump. Haslam *et al*.1993.	CA1320885C
Controlled porosity osmotic enalapril pump. Rork *et al*.1994.	WO1994001093
Osmotic controlled release drug delivery device. Ruddy *et al*.2001.	EP1227800A1
Osmotic controlled release drug delivery device. Ruddy *et al*.2002.	WO200103214A1
Novel multiplying porous osmotic and diffusion drug delivery system. Rudresha *et al*.2005	IN2004MU01385 A20060721
Novel multiplying porous osmotic and diffusion drug delivery system. Prasad *et al*.2007.	IN2005MU00321A 20070330
Controlled porosity osmotic pump based drug delivery system. Chodankar *et al*.2007.	IN2005MU01282 A20070302.

Controlled porosity osmotic pump based drug delivery systems. Roopali *et al*.2008.	IN226882
Controlled porosity osmotic pump tablet of high permeable drugs and the preparation method thereof. Wang *et al*. 2008.	WO2008052417
Salvianolic acid controlled porosity osmotic pump tablets and method of preparing the same. Gao *et al*.2008.	CN200810027661
Novel swellable porous osmotic pump drug delivery system. Pritam *et al*.2009.	IN2007MU01469 A 20090619.
Controlled porosity osmotic pump tablet of high permeable drugs and the preparation method thereof. Wang *et al*.2009.	EP2085078
Porous controlled-onset controlled-release tablet of dilthiazem hydrochloride and its preparation method. Jiang *et al*.2010.	CN101766581 A 20100707.
Controlled porous osmotic pump tablets of high permeable drugs and the preparation process thereof. Wang *et al*.2010.	US20100291208
Surgery controlled release therapeutic device or system implanted dynamic device or system. Eric *et al*.2011.	US20110184389

Table 7- Marketed formulation of controlled porosity osmotic pump

Brand name	API	Strength (mg)	Market Status (US)
Tiamate	Diltiazem Malate	120, 180, 240	Discontinued
Teczem	Enalapril Diltiazem	280 5	Discontinued
Acu System C	Vitamine C	NA	Prescription

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