Research Article

FORMULATION AND OPTIMIZATION OF ACECLOFENAC MONOLITHIC OSMOTIC PUMP

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ABSTRACT

The monolithic osmotic tablet system, which is composed of a monolithic tablet coated with cellulose acetate (CA) and membrane drilled with two orifices on both side surfaces, has been described. The influences of tablet formulation variables including amount of polymer Explotab (Expt), amount of sodium chloride (NaCl), have been investigated. The optimal tablet formulation and the osmotic-suspending co-controlled delivery mechanisms have been proposed. Orifice size and membrane variables including nature and amount of plasticizers as well as thickness on drug release have also been studied. The in vitro release profiles of the optimal system have been evaluated in various release media and different agitation rates, and compared with commercialized conventional tablet. It was found that Explotab was suitable to be thickening agent, both amount of NaCl and amount of Explotab had comparable and profoundly positive effects. It could be found that the optimal orifice size was 800 μm. It has also been observed that hydrophilic plasticizer polyethylene glycol (PEG) improved drug release, when they were incorporated in CA membrane. The monolithic osmotic tablet system was found to be able to deliver Aceclofenac at the rate of approximate zero-order up to 24 h, independent of both environmental media and agitation rate, and substantially comparable with the commercialized conventional tablet. The monolithic osmotic tablet system was simple to be prepared as exempting from push layer and simplifying in the orifice drilling compared with the push–pull osmotic tablet. The monolithic osmotic tablet system may be used in drug controlled delivery field, especially suitable for water-insoluble drugs.

Keywords: Aceclofenac; Osmotic pump; Twenty-four-hour delivery; Monolithic osmotic tablet system; Cellulose acetate membrane.

INTRODUCTION

Osmotic device are the most promising strategy based system for controlled drug delivery. They are the most reliable Controlled Drug Delivery System (CDDS) and could be employed as oral drug delivery system. Osmotic Pump Tablet (OPT) generally consist of a core including the drug and osmotic agent (the drug can also be the osmotic agent), other excipient and semi permeable membrane coat.[1]

Osmotic pressure was first employed as an energy source to deliver active ingredient in 1950's. The pharmaceutical agent can be delivered in a controlled pattern over a long period by osmotic pressure. There has been increasing interest in the development of osmotic device in the past two decades. Various types of osmotic pumps were reviewed by Santus and Bakers[2]. The Elementary Osmotic Pump (EOP) was introduced by Theeuwes in 1970's. The EOP consist of an osmotic core with a drug surrounded by a semi permeable membrane, drilled with a delivery orifice. In operation the osmotic core acts by imbibing water from surrounding medium via the semi permeable membrane. Subsequently the drug solution was formed within the device and delivered out of the device via the orifice. The EOP is very simple to prepare and releases drug at an approximate zero-order rate[3-4]. However, the generic EOP is only suitable for the delivery of water-soluble drugs. To overcome the limit of EOP, a push–pull osmotic tablet was developed in the 1980s. The push–pull osmotic tablet consists of two compartments, one containing drug and the other an osmotic agent and an expandable agent. A semipermeable membrane that regulates water influx into both compartments surrounds the system. An orifice was drilled into the surface of the drug compartment to allow drug release[5-8] (Fig 1). While the push–pull osmotic tablet succeeds in delivering water-insoluble drug, it has two disadvantages: (1) the tablet core is prepared by compressing two kinds of compartments together, a complex technology as compared with that of monolithic tablets; and (2) after coating, a complicated laser-drilling technology should be employed to drill the orifice next to the drug compartment[9].

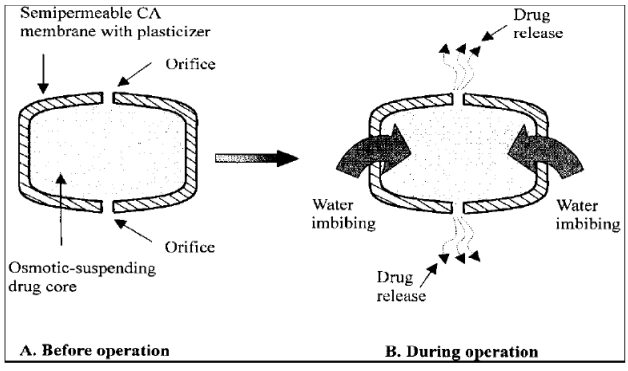


Figure 1: Schematic diagram of the monolithic osmotic tablet system composed of a monolithic tablet surrounded by a CA membrane drilled with two orifices.

The information regarding the effect of tablet formulation variables, orifice size and membrane variables on drug release of this system is less well known. Therefore, the aims of this work were: (1) to study the influences of

tablet formulation variables, such as amount of Explotab, amount of sodium chloride (NaCl) on drug release, and to propose a delivery mechanism and optimal tablet formulation for this system (2) to study the influences of orifice size and membrane variables, including the nature and amount of plasticizer as well as thickness on drug release; (3) to evaluate the in vitro release profile of the optimal monolithic osmotic tablet system in various media and agitation rates; and (4) to compare the in vitro release pattern of the monolithic osmotic tablet system with commercialized products

Aceclofenac was chosen as a model drug, practically insoluble in water a well known and most widely used Non Steroidal Anti Inflammatory Drug and the entire sample were prevented from light.

MATERIAL AND METHODS

Aceclofenac powder (Fourts India Ltd Chennai) which was used as a modeled drug, Sodium chloride (s.d Fine Chemicals Mumbai), Explotab JRS Pharm USA as polymer and thickening agent, Microcrystalline cellulose (MCC) (Loba Chemi Pvt Ltd Mumbai), Magnesium Stearate (s.d. Fine Chemicals, Mumbai), Starch (Loba Chemi Pvt Ltd Mumbai) as a binder, Cellulose-Acetate (Eastman, New Delhi) was used as a semipermeable membrane, Poly Ethylene glycol (Loba Chemi Pvt Ltd Mumbai) as a plasticizer.

Preparation of core tablet

The core containing magnesium stearate as lubricant was prepared by wet granulation technique. The respective powder (drug, polymer and optional additives composition listed in table 1) were blended thoroughly with mortal and pestle. The resultant powder mixture was compressed in rotary tablet compression machine fitted with 12 mm concave punches.

Table 1: The basic tablet formulation and varying range of all chemicals

Formulation code	Explotab	NaCl	Microcrystalline cellulose	Aceclofenac
F1	100	200	00	220
F2	100	200	50	220
F3	100	150	100	220
F4	100	100	150	220
F5	100	50	200	220
F6	75	200	75	220
F7	75	100	175	220
F8	75	150	125	220
F9	150	150	50	220
F10	150	100	100	220
F11	150	50	150	220
F12	50	250	50	220
F13	50	200	100	220
F14	50	150	150	220

Coating and drilling

Tablets were coated by using a pan coater. Cellulose acetate (CA; 4%, w/v) in acetone containing known levels of plasticizer was used as coating solution. The coating conditions were outlined as follows: pan specification, stainless steel, spherical, 300-mm diameter; pan rotating rate 12 rpm, spray rate 10 ml /min; drying, using a heat gun at 40°C to remove residual solvent.

In vitro release test

The *in vitro* dissolution study of Aceclofenac coated tablet was performed using USP Apparatus II (basket) fitted with paddles (100 rpm) at 37±0.5°C using 900 ml of pH 6.8 Phosphate buffer as a dissolution medium for subsequent 24 hrs at the predetermined time interval, 5 ml of aliquots were withdrawn and was replenished by 5 ml of fresh dissolution medium each time. Absorbance of the sample was measured spectrophotometrically at 274 nm.

RESULTS AND DISCUSSION

Effect of tablet formulation variables on drug release

To study the effect of tablet formulation variables on drug release, tablets with various formulations were prepared, subsequently coated, and a circular orifice with a diameter of 800 µm, was drilled on each side of the surface.

Effect of amount of Osmogen

The release profiles of Aceclofenac were used to study the influence of amount NaCl. The release rate increased as the amount of NaCl increased. The more NaCl incorporated into tablet, the more water was imbibed and the more core formulation could be liquefied and, as a consequence, more Aceclofenac was released.

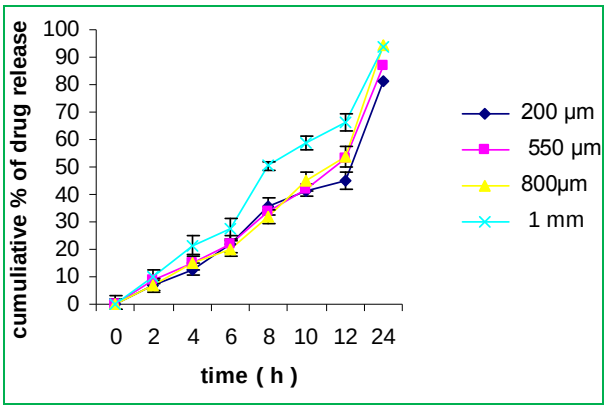
Effect of amount of Explotab

The release profiles of Aceclofenac were used to study the influence of amount of Explotab. It can be observed that amount of Explotab also had a pronounced influence on release profile. Explotab played the role of thickening agent, and elevated the viscosity of the suspension and, subsequently, prevented precipitation of Aceclofenac. The larger the amount of Explotab used, the higher the viscosity of the suspension formed and the higher the stability of the Aceclofenac powder. As a consequence, the release rate decreased as the amount of Explotab increased and vice versa.

Effect of orifice size on drug release profile

It was reported that there was an appropriate range of orifice sizes for EOP; these must be smaller than the maximum limit to minimize the delivery rate made by diffusion through the orifice. Also, they must be larger than a minimum to minimize hydrostatic pressure inside the system[10]. The optimal tablets were coated and subsequently a circular orifice with same diameter was drilled on each side of the surface. Figure 2 & table 2 shows the influence of orifice size on release profile.

Figure 2: Influence of orifice size on drug release profile



The results were in accordance with those of EOP. No significant difference existed in the release profiles for orifice diameters ranging from 800 µm – 1 mm. However, the release was somewhat rapid with an orifice diameter of 800 µm. This may be due to the influence of diffusion from the bigger orifice. On the other hand, a longer lag time and a lower release rate were exhibited at an orifice diameter of 0 mm (i.e., without an orifice). The continuous water influx into the system without an orifice produced an increase in the volume of drug suspension inside the system, therefore leading to an increase in the hydrostatic pressure inside the system. The pressure formed would cause membrane disruption and crack formation on the membrane. Subsequently, drug release was initiated via the crack. As the moment of formation and the size of the crack could not be controlled or predicted, the delivery rate made by diffusion through the system without an orifice was uncontrollable. In the following studies, an orifice diameter of 0.8 mm, which was within the optimal range.

Table 2: student "t" test for orifice diameter

	800 µm	1 mm	550 µm	200 µm
P- value	-	P<0.001	P<0.0085	P<0.002
T – value	-	44.15	40825	12.77
significance	-	YES	YES	YES

Effect of membrane variables on drug release profile

Once the tablet formulation and orifice size were decided, the membrane will be a key factor with relation to release profile of the monolithic osmotic tablet system. The release profiles of the optimal tablet coated by a CA membrane without plasticizer, with 10% (CA, %, w/w) of PEG (C1) and 30% (CA, %, w/w) of PEG-400 are compared to study the influence of the nature of the plasticizer on drug release profile. It was observed that PEG increased release rate, when they were incorporated into the CA membrane. This may be explained by the difference in hydrophilicity of the plasticizers. As PEG is a hydrophilic plasticizer, it could be leached easily and left behind porous structure, which increases membrane permeability and drug release rate.

To study the influence of amount of PEG on drug release profiles, the CA membranes were plasticized with levels of PEG of 0, 10 and 30 %, respectively. Figure 3 & table 3 shows that the increase of PEG level led to an increase of drug release rate.

Figure 3: Influence of plasticizer on drug release profile

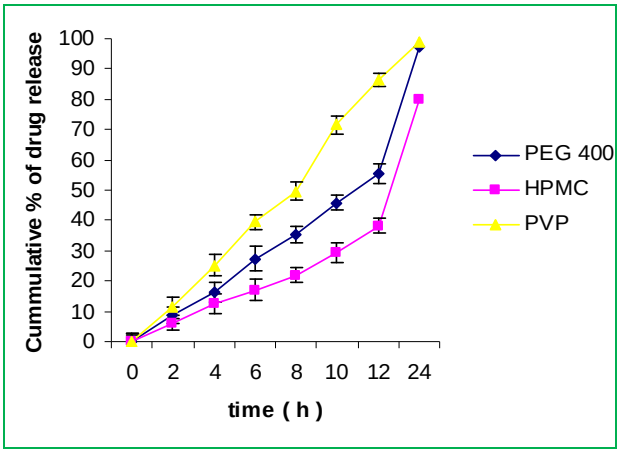


Table 3: student "t" test for plasticizers

	PEG-400	HPMC	PVP
P- value	-	P<0.0001	P<0.0001
T – value	-	60.97	32.20
significance	-	YES	YES

The more PEG incorporated into the CA membrane, the more void space formed after leaching and, in turn, the higher the permeability of the membrane, the higher the drug release rate obtained. To study the influence of membrane thickness on drug release profiles, the optimal tablets were coated to thicknesses of 6.5 %, 10 % and 14 % respectively, using a coating solution with a PEG level of 10%. Figure 4 & table 4 shows that release rate decreased as the membrane thickness increased.

Figure 4: Influence of thickness on drug release profile

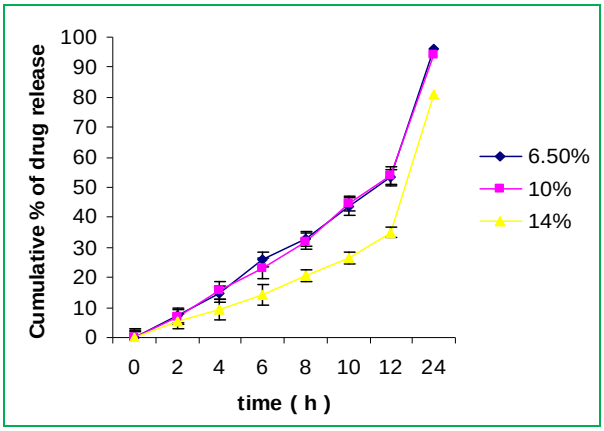


Table 4: student "t" test for thickness

	6.5%	10%	14%
P- value	-	P<0.0001	P<0.0001
T – value	-	15.49	15.49
significance	-	YES	YES

As the thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased and, in turn, the liquification rate of the tablet core decreased, resulting in the drug release rate decreasing. It was found that an approximate zero-order release pattern and appropriate release rate up to 24 h were obtained in the case of the 6.5% coating. The optimal tablet formulation F3 with an orifice size of 0.8 mm was adopted in the following studies to evaluate the monolithic osmotic tablet system.

Discussion of an osmotic-suspension delivery mechanism and optimization of the formulations

Based on the above release profiles it was found that the monolithic tablet system was able to deliver Aceclofenac up to 24 h. However, the system was operated by a somewhat different mechanism from either the generic EOP or the push–pull osmotic tablet. An osmotic-suspension co-controlled delivery mechanism is proposed below. First, the pump was covered in an osmotic mechanism with NaCl as the osmotic agent, because the osmotic pressure difference between the internal system and the external environment was the energy source to imbibe water, which is the basis of all osmotic delivery systems. Meanwhile, the action of another agent, the thickening agent Explotab causes the Aceclofenac powder to be stable in suspension. In operation, water was imbibed from the environment by the osmotic pressure difference between the inside of the tablet and the environment where the tablet is located, which was contributed by the osmotic agent NaCl. Then, a viscous drug suspension was created in situ inside the coated tablet, which resulted from thickening agent Explotab and the imbibed water. The suspension was subsequently pumped out through the orifices. The drug release was co-controlled by both osmotic and suspension mechanisms. It should be pointed out that the stable suspension of drug by use of a thickening agent was equally important as that of the osmotic action.

To optimize tablet formulation, some principles should be obtained. First of all, to make suspension easy, the original drug powder should be micronized. Again, as amounts of both NaCl and Explotab have profound and comparable influence, the amounts of NaCl and Explotab used should be as large as possible, and comparable. Also, a reasonable amount of the disintegrant MCC should be used to increase soluble area. Again, a trace amount of the lubricant, magnesium stearate, should be used to make tablet detach easily from the mold. A relatively high ratio of drug loading / tablet weight was economically favored. All chemicals were used concurrently for the purpose of delivering the water-insoluble drug Aceclofenac at a higher rate up to 24 h. Based on these principles, F3 might be chosen as the optimal formulation for 200 mg Aceclofenac loading. Once the tablet formulation is decided, the drug release of the system will be affected by orifice size and membrane variables. Therefore, the following studies were carried out to investigate the influences of orifice size and membrane variables on drug release profile.

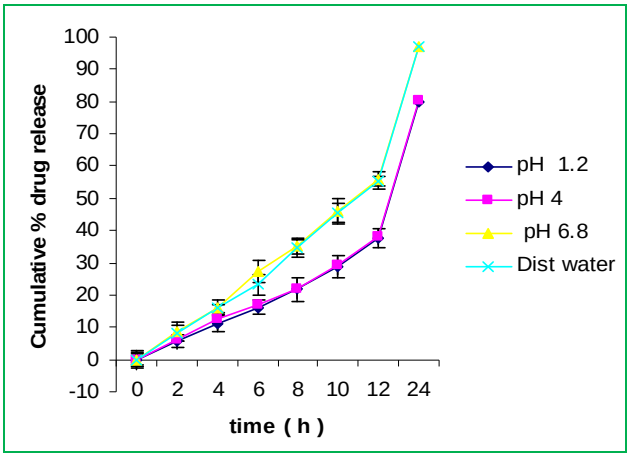
Optimization of the formulation

It was possible to control the release of drug by Monolithic osmotic pump. The different concentration of sodium chloride and explotab was studied in order to optimize the core. Firstly sodium chloride with higher concentration proportionately increases the drug releases due to higher osmotic pressure created inside the system. On the contrary the drug releases was decreasing when the polymer concentration increased. In total, 14 formulations were developed with different concentration of sodium chloride and explotab. The mechanism of drug release in such a device where active ingredient released as tiny droplets from the dispersion of polymer matrix.

Effect of pH on drug release

To investigate the influence of release media on drug release, the release test was conducted in DIW, *pH 1.2, pH 4, pH 6.8* respectively. Fig.5 shows the release profiles of the system in these release media. No significant difference in release profile could be found. In other words, the monolithic osmotic tablet system exhibited a media-independent release. Thus, may be expected that the fluid in different parts of the gastrointestinal tract scarcely affect drug release of the monolithic osmotic tablet system.

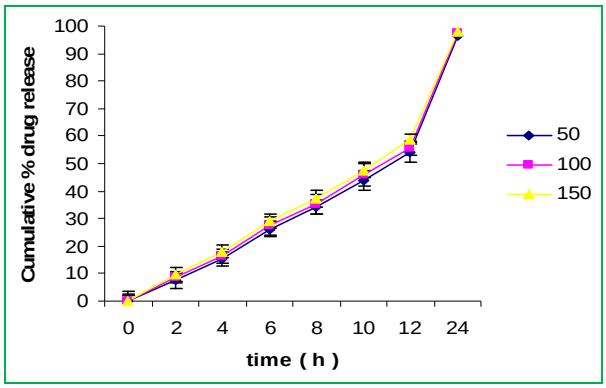
Figure 5: Influence of pH on drug release profile.



Effect of agitation on drug release

To investigate the agitation rate on drug release profile, release tests were carried out at agitation rates of 50, 100 and 150 rpm, respectively[11]. Fig.6 showed that there was no significant difference in release profiles under different agitation rates. Therefore, it might be expected that the mobility of the gastrointestinal tract hardly affects the drug release of the monolithic osmotic tablet system. As drug release was independent of both release media and agitation rate, the monolithic osmotic tablet system might exhibit a comparable *in vitro / in vivo* release profile.

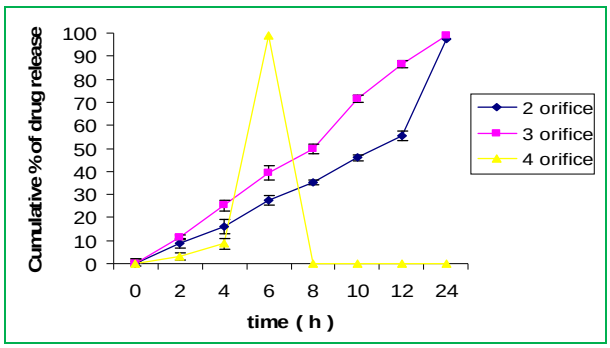
Figure 6: Influence of agitation on drug release



Effect of number of orifice on drug release

Different number of orifice was created (2, 3 and 4), Fig.7 showed that the tablet with 2 orifice released 97.22 % of drug at the end of 24 th hr. The tablet with 3 orifice was found to develop a crack between them and release 99.11% at the end of 20th hr and tablet with 4 orifice was completely burst out and 98 % of drug released at the end of 6th hr. So 2 orifices were kept constant throughout the work.

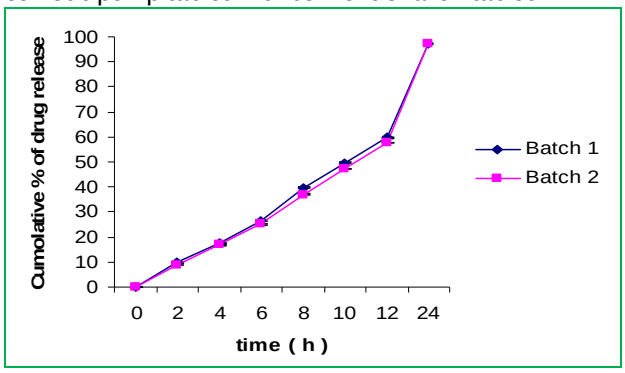
Figure 7: Influence of number of orifice on drug release



Comparison between optimized formula and marketed Aceclofenac SR tablet

Comparison was carried out between optimized formula and marketed Aceclofenac SR tablet by performing the dissolution Fig.8 showed that, the drug release at the end of 24 hr was found to be 97.22% and 95.45% respectively, Hence we can conclude that the drug release was controlled and sustained till 24 hr for the optimized formula and follows zero order release.

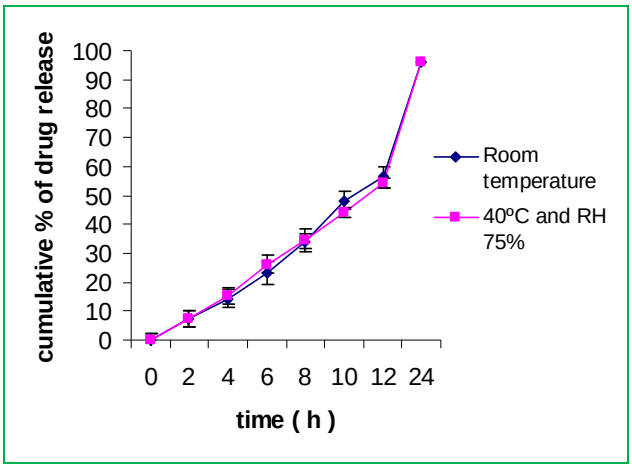
Figure 8: Release rate comparison of the monolithic osmotic pump tablet with conventional SR tablet



Reproducibility of batch

To check the reproducibility of batch different batches were prepared at different time interval. The dissolution was carried out and Fig.9 shows result that the drug release was same at the end of 24 hr.

Figure 9: Reproducibility of optimized batch



Stability study

Three month stability study for optimized formula was carried out at an ambient room temperature which shows no change in physical characters and drug content. Fig.9 shows that in vitro drug study also revealed that there was no much difference in drug release at the end of 24 hr.

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CONCLUSION

The monolithic osmotic tablet system, which is composed of a monolithic tablet coated with a CA membrane with two orifices drilled on both side surfaces, has been studied. The optimal tablet formulation and an osmotic suspension co-controlled delivery mechanism have been proposed. It was found that both NaCl and Explotab had comparable and profoundly positive effects. It could be observed that the optimal orifice size was 800 µm. It has also been found that the hydrophilic plasticizer PEG, improved drug release when they were incorporated in CA membrane. The monolithic osmotic tablet system was found to be able to deliver Aceclofenac at a rate of approximately zero-order up to 24 h, independent of both environmental media and agitation rate, and substantially comparable with the marketed tablets. The monolithic osmotic tablet system was simple to prepare, because there is no need for a push compartment, and is simpler with regard to orifice drilling, compared with the push–pull osmotic tablet. The monolithic osmotic tablet system may be used in the field of controlled delivery of drugs, and is especially suitable for water-insoluble drugs.

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