MODERN ADVANCEMENT IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration, and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend a therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.

KEYWORDS: SRDDS, Drug selection Criteria, Factors affecting SRDDS, Classification.

INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period is measured
in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities. Controlled release systems also denoted systems, which can provide some control whether this be of a temporal or spatial nature or both, of drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Fig. 1: Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release formulation.

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS
1. Reduction in frequency of intakes.
2. Reduce side effects.
3. Uniform release of drug over time.
4. Better patient compliance
5. The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained
6. Better control of drug absorption can be attained, since the high blood level peak that may be observed after administration in an extended action form
7. The characteristic blood level variations due to multiple dosing of conventional dosage form can be reduced.
8. The total amount of drug administration can be reduced, thus
   a) Maximizing availability with minimum dose
   b) Minimize or eliminate local side effects
   c) Minimize or eliminate systemic side effects
   d) Minimize drug accumulation with chronic dosing
9. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients

**DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY**
1. Increased cost.
2. Toxicity due to dose dumping.
4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
5. Increased potential for first-pass clearance.
6. Need for additional patient education and counseling.

**Limitations**
1. If the active compound has a long half-life (over six hours), it is sustained on its own.
2. If the pharmacological activity of the active compound is not related to its blood levels, slow releasing then has no purpose.
3. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
4. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to
avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

5. Not effectively absorbed in lower small intestine.
6. Large doses are required (more than 1 gm).
7. Drug with low therapeutic index.
8. Precise dose to individuals is required.

CHARACTERISTIC THAT MAKES A DRUG UNSUITABLE FOR SR FORMULATION

• Short elimination half-life, i.e., t1/2 <2 hrs
• Long elimination half-life, i.e., t1/2 >4 hrs
• Narrow therapeutic index
• Large doses
• Poor absorption
• Low or slow solubility
• Extensive first-pass clearance.

DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug’s molecular weight, solubility at different pH and apparent partition coefficient (Table 1 and Table 2).

Table 1: Physicochemical Parameters for Drug Selection.

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Parameter</th>
<th>Preferred value</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>Molecular weight/size</td>
<td>&lt;1000</td>
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<tr>
<td>3</td>
<td>Solubility</td>
<td>&gt;0.1 mg/ml for pH1 to pH7.8</td>
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<tr>
<td>4</td>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>5</td>
<td>Release</td>
<td>Should not be influenced by pH and enzymes</td>
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</table>
Table 2: Pharmacokinetic Parameters for Drug Selection.

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Elimination half life</td>
<td>Preferably between 0.5 and 8h</td>
</tr>
<tr>
<td>2</td>
<td>Elimination rate constant</td>
<td>Required for design</td>
</tr>
<tr>
<td>3</td>
<td>Total clearance</td>
<td>Should not be dose dependent</td>
</tr>
<tr>
<td>4</td>
<td>Absolute bioavailability</td>
<td>Should be 75% or more</td>
</tr>
<tr>
<td>5</td>
<td>Apparent volume of distribution Vd</td>
<td>The larger Vd and MEC, the larger will be the required dose size</td>
</tr>
<tr>
<td>6</td>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>7</td>
<td>Toxic concentration</td>
<td>Apart the values of MTC and MEC, safer dosage form. Also suitable for drugs with very short half life.</td>
</tr>
</tbody>
</table>

VARIOUS MECHANISMS OF MEDICAMENT RELEASE

1. Diffusion is rate limiting

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system (Fig. 2).

In practice, we can follow either of the two methods, a. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and released the drug through diffusion. b. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain a constant drug level in blood.

2. Dissolution is rate limiting

The drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it’s possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g.
Polyethylene Glycol. One may skip the use of disintegrating agent to promote a delayed release.

3. Osmotic pressure is rate limiting
Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation.

4. Release is controlled by ion exchange
Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastrointestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.

FACTORS AFFECTING THE FORMULATION OF ORAL SRDDS
There are two major factors that affect the release rate from the DDS. They are:
1. Physicochemical factors
2. Biological factors.

PHYSICOCHEMICAL FACTORS
a. Aqueous solubility
b. Partition coefficient ($P_{o/w}$)
c. Drug pKa and ionization at physiological pH
d. Drug stability
e. Molecular weight and diffusivity
f. Protein binding
g. Dose size.
AQUEOUS SOLUBILITY
Most of the drugs are weak acids or weak bases. Drugs with low water solubility will be difficult to incorporate into SR mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or GI fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to fewer soluble drug. It is often difficult to incorporate a highly water-soluble drug in the dosage form and retard the drug release, especially when the dose is high. The pH-dependent solubility, particularly in the physiological pH range, would be another problem for SR formulation because of the variation in the pH throughout the GI tract and variation in the dissolution rate.

The biopharmaceutical classification system allows estimation of the likely contribution of three major factors which affect the oral absorption.
• Solubility
• Dissolution and
• Intestinal permeability.

Class III (high solubility-low permeability) and Class IV (low solubility-low permeability) drugs are poor candidates for SR dosage form compound with solubility <0.1 mg/ml face significant solubilization obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilization dosing formulation. In general, highly soluble drugs are undesirable for formulation into an SR product.

PARTITION COEFFICIENT
The partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Partition coefficient influences not only the permeation of the drug across the biological membranes but also diffusion across the rate controlling membrane or matrix between the time when a drug is administered, and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (i.e., its membrane permeability) in its apparent oil or water partition coefficient defined as,

\[ K = \frac{C_o}{C_w} \]

Where,
Co = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,
Cw = Equilibrium concentration of all forms in an aqueous phase.

In general, drugs with an extremely large value of K are very oil soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug is generally defined by the Hansch correlation, which describe a parabolic relationship between the logarithms of its partition coefficient.

**DRUG PKA AND IONIZATION AT PHYSIOLOGICAL PH**

Drugs existing largely in an ionized form are poor candidates for oral SRDDS. Absorption of the unionized drugs is well whereas permeation of ionized drug is negligible because the absorption rate of the ionized drug is 3-4 times less than that of the unionized drug. The pKa range for an acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for a basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%.

**DRUG STABILITY**

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. Drugs that are unstable in gastric pH can be developed as slow release dosage form and drug release can be delayed until the dosage form reaches the intestine. Drugs that undergo gut wall metabolism and show instability in the small intestine are not suitable for SR system. In such case, the drug can be modified chemically to form prodrugs, which may possess different physicochemical properties or a different route of administration should be chosen.

**MOLECULAR WEIGHT AND DIFFUSIVITY**

Diffusivity is defined as the ability of a drug to diffuse through the membrane. Diffusivity depends on size and shape of the cavities of the membrane. The diffusion co-efficient of intermediate drug molecular weight is 100-400 Daltons; through flexible polymer range is 10–6-10–9 cm²/seconds. Molecular size or weight is indirectly proportional to the diffusibility. Drugs with larger molecular size are a poor candidate for oral SR system.

**PROTEIN BINDING**

It is well-known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part re-circulated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged
release profile, especially if a high degree of drug binding occurs. The drug interaction and the period of binding with mucin-like protein also influence the rate and extent of oral absorption.

**DOSE SIZE**
For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 g is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in the administration of large amounts of a drug with narrow therapeutic range.

**BIOLOGICAL FACTORS**
a. Absorption
b. Distribution
c. Metabolism
d. Biological half-life/duration of action
e. Margin of safety/therapeutic index
f. Side effect
g. Disease state.

**ABSORPTION**
The constant blood or tissue concentration of drug can be obtained from the oral SR systems through uniform and consistent release as well as absorption of the drug. The desirable quality of the sustaining system is that it should release completely absorbed. Apparently, the release of the drug from the system is the rate limiting step, where rapid absorption relative to the drug release is always expected, i.e., Kr << Ka.

If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hrs, the maximum half-life for absorption should be approximately 3-4 hrs. Otherwise, the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for the low extent of absorption are poor water solubility, small partition co-efficient, protein binding, acid hydrolysis and metabolism or site specific or dose-dependent absorption. Drugs with the high apparent volume of distribution, which influence the rate of
elimination of the drugs, are a poor candidate for oral SRDDS. A drug which extensively metabolizes is not suitable for SRDDS. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is the poor candidate for SR delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in the lumen or the tissues of the intestine, can show decreased bioavailability from the sustained releasing systems.

**DISTRIBUTION**

The distribution of drug molecules into the tissue and cells can be the primary factor in particularly drug elimination kinetics. Since it not only lowers the concentration of circulating drug, but it also can be rate limiting in its equilibrium with blood and extra vascular tissue. The distribution includes the binding of the drug to the tissues and blood proteins. Protein-bound drugs molecules are considered as inactive and unable to permeate biological membranes, and a high degree of protein binding provides prolonged therapeutic action. The apparent volume of distribution is one of the important parameters of the drugs that describe the magnitude of distribution as well as protein binding within the body. The apparent volume of distribution is the proportionality constant of the plasma concentration of the drug to the total drug amount in the body. Thus for the design of sustain release products, one must have information of the disposition of drug.

**METABOLISM**

Metabolism of the drug is either an inactivation of an active drug or conversion of an inactive drug to an active metabolite. Metabolism of the drug occurs in a variety of tissues, which are containing more enzymes. Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolites. The formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

Drugs that are capable of either inducing or inhibiting enzyme synthesis, they are the poor candidate for SR delivery system due to difficulty in maintaining uniform blood levels.
Drugs possessing variation in bioavailability due to the first-pass effect or intestinal metabolism are not suitable for SRDDS.

BIOLICAL HALF-LIFE/DURATION OF ACTION

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The duration of action significantly influences the design of oral SR delivery system and it is dependent on the biological half-life. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half-lives required frequent dosing to minimize fluctuations in the blood levels. SR dosage forms would appear very desirable for such drugs. For a given steady state drug concentration, the zero-order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus drug with very short half-lives require faster rate of release, for a modest duration of time while dosage form requires large dosage. In general, drugs with half-lives shorter than 2 hrs are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already sustained.

MARGIN OF SAFETY/THERAPEUTIC INDEX

Margin of safety of a drug can be described by considering therapeutic index, which is the ration of median toxic dose and median effective dose.

Therapeutic index = TD50/ED50

A drug is considered to be relatively safe with therapeutic index more than 10 i.e., larger the ratio the more safely is the drug. Margin of the safety of the drugs determined on the basis of therapeutic index is the range of plasma concentration in which the drug is considered to the safe and therapeutically effective. The drugs with narrow therapeutic indices the release pattern should be more precise to maintain the plasma concentration within the narrow therapeutic and safety range. The unfavorable therapeutic index of a drug can be overcome by suitable employment of the SR mechanisms.

SIDE EFFECT

The side effects of the some drugs are mainly developed due to fluctuation in the plasma concentrations. The incidences of side effects can be minimized by controlling the concentration within therapeutic range at any given time. The SR drug delivery is the most widely used to incidences of the GI (local) side effects rather than a systemic side effect of
the drug. The drug properties which induce local or systemic side effect can be circumvented or modified by their incorporation in a suitable oral SR delivery system that employs a specific controlled release mechanism.

**DISEASE STATE**

Disease state and circadian rhythm are not drug properties, but they are equally important as drug properties in considering a drug for SR. For example:

- Aspirin is a drug of choice for rheumatoid arthritis though it is not suitable for SR dosage form. Still, aspirin SR dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.
- Asthma attacks are commonly occurring before bedtime, due to a low cortisol level. The highest cortisol level occurred between 12 midnight and 4 a.m. These variations entail for the design an oral SR delivery in accordance to circadian rhythm.

**CLASSIFICATION OF SRDDS**

A. Diffusion sustained system
   a. Reservoir type
   b. Matrix type
B. Dissolution sustained system
   a. Reservoir type
   b. Matrix type
C. Methods using Ion-exchange
D. Methods using osmotic pressure
E. pH-independent formulation
F. Altered density formulation

**DIFFUSION SUSTAINED SYSTEM**

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Basically, diffusion process shows the movement of drug molecules from a region of a higher concentration to one of the lower concentration. The flux of the drug J (in amount/area−time), across a membrane in the direction of decreasing concentration is given by Fick’s law.

\[ J = -D \frac{dc}{dx} \frac{L}{L} \]

\( D = \) diffusion coefficient in area/time
\( \frac{dc}{dx} = \) change of concentration “c” with distance “x”
Reservoir type
In the system, water insoluble polymeric material encases a core of drug. The drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. The additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media (Fig. 3).

Matrix type
In a matrix system, the drug is dispersed as solid particles within a porous matrix formed of a water-insoluble polymer. The drug particles located at the surface of the release unit will be dissolved first and drug release rapidly. Thereafter, drug particles at a successively increasing distance from the surface of the release unit will be dissolved and release by the diffusion in the pores to the exterior of the release unit. Thus, the diffusion distance of dissolve drug will increase as the release processes proceeds (Fig. 4).

DISSOLUTION SUSTAINED SYSTEM
A drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. SR preparation of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drugs with slowly dissolving materials or
incorporating it into a tablet with a slowly dissolving carrier. Dissolution sustained system can be made by different ways.

**METHODS USING ION-EXCHANGE**[30]

Ion-exchange systems generally use resins composed of water-insoluble cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

\[
\text{Resin}^+ - \text{drug}^- + \text{X}^- \rightarrow \text{Resin}^+ - \text{X}^- + \text{drug}^- \\
\text{Resin}^- - \text{drug}^+ + \text{Y}^+ \rightarrow \text{Resin}^- - \text{X}^+ + \text{drug}^+ \\
\text{Where,} \, X^- \text{ and } Y^+ \text{ are ions the GI tract.}
\]

The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusion path length, and rigidity of the resin, which is the function of the amount of cross-linking agent used to prepare the resin. For the better release in this system is to coat the ion-exchange resin with hydrophobic rate-limiting polymer.

Fig. 5: Schematic representation of diffusion sustained drug release: ION-EXCHANGE.

**SR FORMULATION BASED ON OSMOTIC PRESSURE**

In this system, the flow of liquid into the release unit driven by a difference in osmotic pressure between the inside and the outside of the release unit is used as the release-controlling process. In osmosis SR system, the following sequences of steps are involved in the release process.

- Osmotic transport of liquid into the release unit.
- Dissolution of the drug within the release unit.
- Convection transport of a saturated drug solution by pumping of the solution through a single orifice or through pores in the semi-permeable membrane.

![Figure 6. Schematic representation of osmotic system Type-A and Type-B](image)

**PH-INDEPENDENT FORMULATION**

Since most drugs are either weak acids or weak bases, the release from SR formulations is pH-dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH-independent drug release. A buffered SR formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming a polymer. When GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

**ALTERED DENSITY FORMULATIONS**

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of DDS in the GI tract.

**High-density approach**

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore, be at least 1-4 g/cm³.
Low-density approach
Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of the drug for SR purpose.

Some marketed sustained release formulations

Table 1: List of some marketed sustained release formulations.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Brand name</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reservoir system tablet</td>
<td>Kadian®</td>
<td>Morphine sulfate</td>
</tr>
<tr>
<td>Matrix system tablet</td>
<td>Oramorph®</td>
<td>Morphine sulfate</td>
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<tr>
<td></td>
<td>Imdura®</td>
<td>Isosorbite mononitrate</td>
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<td></td>
<td>K-TAB®</td>
<td>Potassium chloride</td>
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<td>Glucomet® SR</td>
<td>Metformin HCl</td>
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<td></td>
<td>BIAxin® XL</td>
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<td>Ambien CR</td>
<td>Zolpidem tartarate</td>
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<td>Diffusion controlled release</td>
<td>Welbutrin XL</td>
<td>Bupropion</td>
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<tr>
<td>Elementary osmotic pump system</td>
<td>Efidac 24®</td>
<td>Chlorpheniramine meleate</td>
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<td>Acutrim</td>
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<td>Minipress XL</td>
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<td>Push pull osmotic system</td>
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REFERENCES


