ABSTRACT
Sustained drug delivery system is one of the most useful tools that providing promising approaches to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration level of the drug in the body. The basic goals of sustained drug delivery system are to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in order to maximize the utility, such a way that efficiency is maximized, reduced the side-effects and cure of the disease is achieved. Sustained release drug delivery is improve patient compliance by reduction frequency of drug administration, reduction steady-state fluctuation of drug levels, increased safety margin of low therapeutic index drug, maximum utilization of the drug, reduction in healthcare costs through improved therapy and shorter treatment period. Tablets offer the lowest cost approach to sustained and controlled release dosage forms. Matrix tablets serves as an important tool for oral extended- release dosage. Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers. The availability of different classes of polymers in controlling the release of drugs has become the most important aspect in the formulation of matrix tablets. The release of drug from matrix drug delivery systems by both dissolution-controlled as well as diffusion controlled mechanisms.

KEYWORDS: Sustained release, controlled release, matrix tablet, hydrophobic polymer and hydrophilic polymer.
INTRODUCTION
The delivery of accurate drug concentration to the site of action in order to achieve appropriate therapeutic effect or response in the body is the key objective of the drug delivery systems\(^1\). There are two types of delivery systems which are generally used. Conventional drug delivery systems or the immediate release drug delivery systems are the systems which are categorized by the quick and unhindered drug release rate and release kinetics. Modified-release drug delivery systems are the other type. In order to achieve definite therapeutic responses, there is an alteration in the rate, site and kinetic performance of the API released inside the body in these types of drug delivery systems. These include: Targeted drug delivery systems, delay or repeated drug delivery systems and prolonged or extended drug delivery systems (Controlled release, Sustained release and long-acting dosage forms)\(^2\). In this review article, we selected sustained release drug delivery matrix system, hence only this topic will be focused in detail.

Sustained release tablets and capsules are commonly taken only once or twice daily, as compared with counterpart conventional forms that may have to be taken three or four times daily to attain the same therapeutic effect. Sustained-release formulations provide an immediate release of drug that produces the desired therapeutic effect, followed by a gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained release dosage form provided sustained drug levels in plasma that often eliminates the need for night dosing, which benefits not only the patients but the care giver as well. There is a growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. In addition, there is a high interest for design a dosage product that allows high drug loading, particularly for drugs with high water solubility. The oral administration is the most popular route used for sustained release delivery due to ease of administration, convenience, greater flexibility in dosage form design, ease of production and low cost of production of such a system. Solid dosage forms are the most of the sustained release delivery systems for oral use and based on diffusion, dissolution or a combination of both mechanisms for the control of drug release\(^3\).

PERORAL SUSTAINED RELEASE FORMULATION
Peroral sustained release formulations are defined as formulations from which the drug release is controlled over a certain period of time. They are intended for administration via the oral route. Terms such as controlled-release, prolonged-action, repeat action and
extended-release have also been used to describe such dosage forms.

THE RATIONALE FOR DEVELOPING SUSTAINED RELEASE\cite{4}
1. To extend the duration of action of the drug.
2. To minimize the fluctuation in plasma level.
3. To reduce the frequency of dosing.
4. Improved drug utilization.
5. Less adverse effects.

ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS\cite{5,6}
1. Improve patient compliance.
2. Reduced drug plasma level fluctuation.
3. Reduction the total dose.
5. Reduction the cost of treatment.

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS\cite{7,8}
1. Dose dumping may occur with the faulty formulation.
2. More cost than conventional dosage form.
3. Reduced potential for dose adjustment.
4. Increased potential for first-pass metabolism.
5. Possible reduction in systemic availability.
6. Poor in vivo and in-vitro correlations.

PERORAL SUSTAINED RELEASE FORMULATION DESIGN STRATEGY
Peroral sustained release formulations according to the mechanism of drug release can be classified into following classes
1. Dissolution controlled extended release formulations.
   a) Matrix dissolution control.
   b) Reservoir dissolution control.
2. Diffusion controlled sustained release formulations.
   a) Matrix diffusion control.
   b) Reservoir diffusion control.
3. Osmotic-controlled sustained release formulations.
4. Sustained release formulations based on ion exchange resin.
5. pH– independent release formulations.

**MATRIX TABLET**

Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices. The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the retardant. Alternatively, drug, retardant blend and other additives may be granulated prior to compression. These systems release the drug in a continuous manner by dissolution-controlled and diffusion-controlled mechanisms\[9,10\].

**Advantages of matrix systems**\[11\]

- Easy to manufacture.
- Versatile, effective, low cost.
- Can be made to release high molecular weight compounds.
- Accidental leakage of the total drug component is less likely to occur.

**Disadvantages of the matrix systems**

- The remaining matrix must be removed after the releasing of the drug.
- Greater dependence on GI residence time of dosage form.
- Delay in the onset of drug action.
- Increased potential for the first-pass metabolism.
- Release rates of the drug are affected by food and the rate transit through the gut.
- The drug release rates vary with the square root of time.

**CLASSIFICATION OF MATRIX TABLETS**

(A) On the basis of retardant material used

1. **Hydrophilic matrix tablet**\[12\]

Hydrophilic matrix may be formulated by a wet granulation of the drug and hydrophilic matrix materials or by direct compression of the blended mixture of active ingredient and certain hydrophilic carriers. The hydrophilic matrixes offer several advantages, such as ease of manufacture, cost effectiveness, uniformity of matrix tablets and broad regulatory acceptance. When immersed in fluid the drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The best choice to use in a hydrophilic matrix tablet
formulation is the matrix building material with fast polymer hydration capability. An insufficient polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for the formulation of water soluble drug. Various polymers used for preparation of hydrophilic matrices are tabulated in Table 1.

Table 1: The polymers used in the preparation of hydrophilic matrices.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose derivatives</td>
<td>Hydroxypropylmethylcellulose (HPMC)25,100,4000 and 15000 cps, Hydroxyethylcellulose(HEC), Sodium carboxymethyl cellulose and Methylcellulose 400 and 4000 cps.</td>
</tr>
<tr>
<td>Natural or semisynthetic polymers</td>
<td>Agar-agar, Carob Gum, Alginites, Molasses, Polysaccharides of galactose and mannose, Chitosan and Modified starches.</td>
</tr>
<tr>
<td>Polymers of acrylic acid</td>
<td>Carbopol 934</td>
</tr>
<tr>
<td>Other hydrophilic materials</td>
<td>Alginic acid, gelatin and natural gums</td>
</tr>
</tbody>
</table>

2. Hydrophobic matrices (Plastic matrix tablet)

Sustained release tablets based upon an inert compressed hydrophobic matrix have been used widely. In plastic matrix, usually, the drug release is delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles[13].

In the hydrophobic matrix tablets, the active drug is dispersed in a tablet within a porous skeletal structure by direct compression of the drug with plastic materials provided the plastic materials can be granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be achieved by:

a) The drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agents in an organic solvent and then granulated.

b) The drug can be dissolved in the plastic by an organic solvent and granulated upon evaporation of the solvent.

c) Using latex or pseudo-latex as granulating fluid to granulate the drug and plastic masses.

For example: Polyvinyl Chloride, Ethylcellulose, Cellulose acetate and Polystyrene[14].

3. Fat-wax matrix tablet

The drug can be incorporated into fat wax granules by spray congealing in the air, blend congealing in an aqueous media with or without the aid of the surfactant and spray-drying
techniques. By bulk congealing method, a suspension of drug and melted fat wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and other additives also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized – bed and steam jacketed blender or granulating with a solution of waxy material or other binders\textsuperscript{[15]}.

4. Biodegradable matrices
These consist of the polymers which composed of monomers that linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by the living cells or by non – enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as poly anhydrides and aliphatic polyesters\textsuperscript{[16]}.

5. Mineral matrices
These type of matrices is consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds by the use of dilute alkali\textsuperscript{[17]}.

(B) On the basis of porosity of matrix\textsuperscript{[18]}
According to their porosity matrix systems cn be classified as

1. Macroporous systems
In these systems, the drug diffusion occurs through pores of the matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Microporous system
In this system, drug diffusion occurs essentially through pores. In microporous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non - porous system
These systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

(C) On the basis of the way of matrix preparations
1. Floating matrix system
In this type of matrix system, the bulk density of the matrix is lower than the gastric fluid in
the stomach. After creating buoyancy in the stomach, the release of drug molecules from the matrix can occur slowly, which prolongs gastric residence time and thereby increases the bioavailability of fast release drug molecules\[19\].

2. pH sensitive matrix system
In this type of matrix system, an enteric coating of the matrix system can provide protection for the drug from the harsh acidic media of the stomach. Thus, low pH sensitive drug molecules can reach the small intestine and colon safely. This matrix system works by releasing the enteric coated drug at a specifically high pH value in the GIT, where drug absorption can occur in the right location. PH sensitive polymers such as HPMC- phthalate or cellulose acetate phthalate can be used in this type of matrix system\[20\].

3. Mucoadhesive matrix system
Mucoadhesive matrix systems are designed to enable prolonged retention in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability. In this type of matrix system, the release of the drug is controlled over a period of time. The targeted tissues can be gastrointestinal, buccal, ocular, nasal, respiratory, rectal, urethral and vaginal tissues. In addition, this type of matrix system can be applied to any mucosal tissue in the body. The used materials in this system are swellable hydrophilic polymers which can interact with the glycoproteins being available in the mucous layer of the gut\[21\].

CHARACTERISTICS THAT MAKE DRUGS SUITABLE FOR SUSTAINED RELEASE MATRIX

(A) Biological characteristics\[1,22\]

1. Biological Half-Life
The active therapeutic drugs with short half-lives are excellent candidates for sustained release formulations since this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release formulations. Drugs with long half-lives, more than 8 hours, are also generally not used in sustained release formulations, since there effect is already sustained.

2. Absorption
The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Drugs that demonstrate true lower
absorption rate constants will be poor candidates for sustaining the system.

3. Distribution
Drugs with a high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral sustained release formulations e.g. Chloroquine.

4. Metabolism
Metabolism of drugs 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 a complete conversion of the drug to its metabolites.

(B) Physicochemical characteristics\(^{[23,24]}\)

1. Dose size
In general, a single dose of 0.5-1.0 gm is considered maximal for a conventional dosage form to be administered orally. This also holds for sustained-release dosage forms.

2. Aqueous solubility
Drugs with very low solubility (less than 0.01mg/ml) are inherently sustained. 0.1 mg/ml is considered the lower limit for the solubility of a drug to be formulated in a sustained-release system, therefore the solubility of the drug will limit the choice of mechanism to be employed in the sustained delivery system.

3. Partition coefficient
In the time period between drug administration and its elimination from the body, the drug must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. Drugs with low partition coefficient easily permeate through biological membrane. While drugs with high partition coefficient will either readily penetrate into membrane producing an accumulation in body tissue with subsequent slow elimination.

4. Stability
Drugs administered orally can be subject to both acid-base hydrolysis and enzymatic degradation. Systems that prolong delivery over the entire course of transits in the GI tract are beneficial for drugs that are unstable in the stomach. Drugs that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining
dosage form. This is because more amount of the drugs are delivered in the small intestine and, hence, is subject to degradation.

5. Protein binding

Many drugs can bind to plasma proteins with concomitant influence on the duration of drug action. Binding of drug to the protein can serve as the depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

MATHEMATICAL MODELING OF DRUG RELEASE FROM MATRIX SYSTEM

Mechanism of drug transport from matrix system based on drug diffusion and polymer relaxation/dissolution\[25\]. Fick’s first and second low demonstrates diffusion of the drug through the medium. There are several mathematical models proposed for drug diffusion from matrix system based on these laws.

Huguchi model.

\[ Ft = Q = KH \times t^{1/2} \]  
Where, \( Ft \) = the fraction of dose release at time \( t \).  
\( KH \) = Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Korsmeyer-Peppas model.

\[ \frac{M_t}{M_\infty} = Kt^n \]  
Where, \( \frac{M_t}{M_\infty} \) = the fraction of drug released at time \( t \),  
\( K \) = the release rate constant And \( n \) = the release exponent.

In this model, the value of \( n \) characterizes the release mechanism of the drug as in Table 2. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time\[26\].

Table 2. Release exponent values and related drug release mechanism.

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Mechanism of drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1</td>
<td>Anomalous transport</td>
</tr>
<tr>
<td>1</td>
<td>Case-II transport</td>
</tr>
</tbody>
</table>
Polymers used in matrix tablet

Various polymers that used for the preparation of matrix tablet are tabulated in Table 3.

Table 3. The polymers most widely used in preparing matrix system\textsuperscript{[2]}.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic Polymers</td>
<td>Hydroxylpropylmethyl cellulose (HPMC), hydroxylpropyl cellulose (HPC), hydroxylethyl cellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide), cross-linked homopolymers and copolymers of acrylic acid.</td>
</tr>
<tr>
<td>Hydrophobic Polymers</td>
<td>Polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.</td>
</tr>
<tr>
<td>Waxes</td>
<td>Carnauba wax, candelilla wax, beeswax, microcrystalline wax and paraffin waxes</td>
</tr>
<tr>
<td>Insoluble polymers</td>
<td>Ammoniomethacrylate copolymers (Eudragit RL100, RS100), ethyl cellulose, cellulose acetate propionate, cellulose acetate butyrate, and latex dispersion of methacrylic ester copolymers</td>
</tr>
</tbody>
</table>

FACTORS AFFECTING DRUG RELEASE FROM MATRIX SYSTEMS

Drug-related factors

1. Drug solubility

Diffusion of the drug depends upon the concentration gradient across the medium which is a function of solubility thus a drug with high solubility shows faster release while poorly water soluble drugs (< 0.01 mg/ml) often result in the incomplete release because of their poor solubility and dissolution rate in the matrix. Polymer erosion is more predominates in the case of the matrix with insoluble drugs, while with soluble drugs a combination of diffusion and erosion determine the release of the drug. Drugs that exhibit pH-dependent solubility particularly in gastrointestinal pH range are poor candidate for matrix system\textsuperscript{[25,27]}.

2. Dose/drug content

Drugs with a large dose size (> 500mg) are difficult to formulate into a matrix system because of the requirements of high amounts of the polymer as well as other matrix formers (excipients). An increase in drug content at a constant polymer content increase the rate of drug release due to higher drug concentration and thus higher concentration gradient at the diffusion front\textsuperscript{[25]}. 
3. **Molecular weight and size**

Drugs with a molecular weight of >5000 Dalton are thought to have poor diffusion through the hydrophilic matrices due to the constrain imposed by the aqueous gel structure\[^{28}\].

4. **Particle size and shape**

Particle size and shape of soluble drugs also influence of drug release because of difference in effective surface area and thus intrinsic dissolution rate\[^{29}\].

**Polymer-related factors**

1. **Polymer type**

Type of polymer significantly affects the release of the drug from the matrix. Polymers that used in development of extended release matrix can be classified into water-soluble and water-insoluble polymers\[^{30}\].

2. **Polymer viscosity grade**

At a fixed polymer level, the viscosity of polymer selected controls performance of the matrix by affecting the diffusional and mechanical characteristics of the gel layer. Polymers with Higher viscosity grades are fast hydrating and form a mechanically stable gel layer. Fast hydrating polymers show rapid gel development, limiting initial dose dumping from a matrix and extending the period of release\[^{31,32}\].

3. **Polymer proportion**

The release profile of the drug from matrix system can be varied with different levels of polymers. An increase in polymer level increases the viscosity of the gel layer and thus increases the diffusional path length. This could decrease the diffusion co-efficient of drug result in a reduction in drug release\[^{33}\].

4. **Polymer particle properties**

It was found that decreasing particle size caused a smaller burst effect and induced lag times. The explanation was based on a faster swelling of the smaller particles that allowed a rapid establishment of the gel barrier\[^{34}\].

5. **Polymer combination**

A combination of polymers can result in synergistic retardation of drug release from matrix tablets. This synergism may be due to molecular physical interaction between the individual polymers\[^{35}\].
Formulation related factors

1. Formulation geometry (Size and Shape of tablet)

Both the size and the shape of a tablet formulated as a matrix system exhibiting both diffusional and erosional release can affect the drug dissolution rate. Tablet matrices should be manufactured to be as spherical as possible, in order to produce the minimum release rate, with regard to tablet shape[^36].

2. Process variables

It has been reported that the release of metoprolol tartrate from the formulations developed using direct compression technique was faster than that obtained from formulations developed using the fluid-bed and high-shear granulation techniques. Increasing the compression force significantly effect on the hardness and thickness of the tablets[^33].

3. Formulation Additives

Preformulation studies of the possible interaction between excipients in the solid dosage forms are necessary because these interactions can affect the drug release and bioavailability. Addition of soluble fillers enhances the dissolution of soluble drugs by decreasing the diffusional path length, while insoluble fillers affect the diffusion rate by blocking the surface pores of the tablet[^37].

METHODS OF PREPARATION

1. Direct Compression

In this process, powdered materials are compressed directly without changing the properties of the drug like physical and chemical.

2. Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of the granulating agent. After enough cohesiveness was obtained, the mass is sieved through 22/44 mesh. The granules are dried at 40°C and after that kept in a desiccator at room temperature. Once the granules dried are retained on 44 meshes were mixed with 15% of fines. Lubricants and Glidants are added and the tablets are compressed using a tablet compression machine[^38].

3. Melt Granulation

This substance can be added in the molten form over the substrate, which is then heated
above its melting point. In melt granulation, meltable substance act as liquid binding agent and hence does not require the use of organic solvents. Various lipophilic binders such as Glyceryl Palmitostearate were used in melt granulation technique[39].

**EVALUATION TEST FOR SUSTAINED RELEASE MATRIX TABLETS**[40-42]

1) **Weight variation test**

To study weight variation, twenty tablets of the prepared formulation were weighed using an electronic balance and the average weight is calculated and the test was performed according to the official method.

2) **Uniformity of weight**

Every individual tablet in a batch should be of uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg. Weight control is based on a sample of 20 tablets.

3) **Dimensions**

The dimensions (diameter and thickness) were then determined to within ± 0.01 mm by using digital vernier calipers.

4) **Hardness**

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability.

5) **Friability**

The friability of the matrix tablets was measured by a Roche friabilator. Tablets of a known weight (W0) or a sample of tablets is dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Permitted friability limit is 1 % w/w. Percentage friability was calculated from the weight loss by the following equation.

\[
\text{% Friability} = \frac{W0 - W}{W0} \times 100
\]

6) **In-vitro dissolution study**

The release rate of matrix tablet was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml solvent and set RPM. A sample of the solution was withdrawn from the dissolution apparatus at different time interval. The samples were replaced with fresh dissolution
medium of the same quantity. The samples were filtered through a membrane filter. The absorbance of these solutions was measured using a UV is double beam spectrophotometer.

CONCLUSION
This review article has been focused on the sustained release matrix tablets, advantages and disadvantages and the various polymers used to formulate such system. From the above discussion, we can conclude that sustained release matrix tablet can overcome the problems of conventional oral drug delivery, improve patient compliance and improve the efficiency of the dosage form. The various matrix forming polymers can be successfully used to prepare matrix tablets, releasing the drug in a controlled manner. Simple method for formulation of matrix tablet with cost effectiveness. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

ACKNOWLEDGEMENT
Great thanks to the Faculty of Pharmaceutical Science, Aden University, for providing the required facilities for the completion of this article.

CONFLICT OF INTEREST
All authors declare that there is no conflict of interest.

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