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## Review Article

### PATENTED PHARMACEUTICAL ORAL CONTROLLED RELEASE MATRIX SYSTEM

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#### Abstract

Oral controlled release drug delivery system becomes a very promising approach for those drugs that are given orally but having the high dosing frequency and shorter half-life. Matrix tablets serves as an important tool for oral controlled release dosage forms. Problems like patient compliance, drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels, associated with their counterparts, the conventional dosage forms were rectified. Many of the pharmaceutical dosage form are formulated as sustained release dosage form to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its plasma profile is sustained in duration. Tablets offer the lowest cost approach to controlled and sustained release dosage forms. Matrix tablet as controlled release has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. This review focuses on the various types of matrix systems based on polymer used and porosity of matrix system i.e. hydrophilic, hydrophobic, fat wax, porous, non-porous, pH sensitive. An effort has been made to consolidate different types of patents granted across the globe for last thirty years in the field of matrix system viz. tablet, pellets etc.

**Keywords:** Hydrophilic Polymer, Matrix system, Novel Drug Delivery System, Patents, Controlled Release

## INTRODUCTION

Matrix tablets is a promising approach for the establishment of extended and controlled release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the “oral solid dosage forms in which the active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrix (as shown in Figure 1) which serves as release rate retardants procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the formulation”<sup>1</sup>. These systems release drug in continuous manner by diffusion-controlled and dissolution-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes<sup>2</sup>. Matrix tablets as sustained release (SR) has given a new invention for novel drug delivery system (NDDS) in the field of pharmaceutical technology.

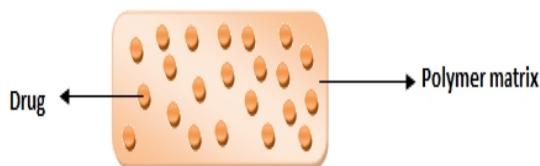


Figure 1: Prototype Matrix System

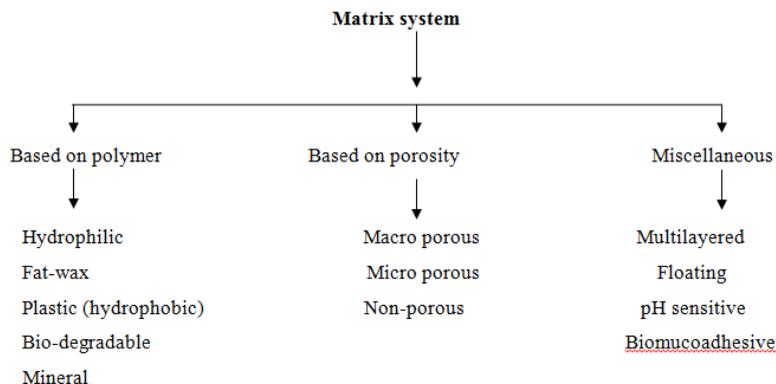
## Pros of sustained release matrix system

Reduced frequency of drug administration, improved patient compliance, reduced blood level oscillation as in multiple dosing with conventional dosage forms and increase in safety margins of high potency drugs along-with the reduced incidence of both local as well as systemic adverse side effects in sensitive patients<sup>3</sup>. The system further leads in the improvement of the ability to provide special effects like morning relief of arthritis through bed time dosing, minimize drug accumulation with chronic dosing, reduction in toxicity by slowing drug absorption and minimize the local and systemic side effects.

## Cons of sustained release matrix system

Greater dependence on Gastro Intestinal residence time of dosage form, increased potential for first-pass metabolism, probability of dose dumping, reduced potential for dose adjustment, increase potential for first pass metabolism and higher cost than convention dosage forms turn down the suitability of this system. Requirement of additional patient education for proper medication, decreased systemic availability and poor *in vitro* and *in vivo* correlations than conventional dosage forms are certain limitations associated with matrix system<sup>2,3</sup>.

## Classification of Matrix System



### Matrix System Based on Polymer Used Hydrophilic Matrix System

Hydrophilic matrix systems are presently one of the most interesting drug delivery systems. They are most widely used to control the release rate of drugs because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Hydrophilic matrix tablets may be defined as “Homogeneous dispersion of drug molecules within Hydrophilic polymers”<sup>2</sup>. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including excellent uniformity of matrix tablets and ease of manufacture. Upon immersion of drug, release is controlled by a gel diffusion barrier that is formed and then tablet erosion<sup>4</sup>. Prykhodko, RN, *et al* 2011 developed a trimetazidinedihydrochloride-containing medication in the form of a 12-hour extended-release matrix tablet containing: 45.4 to 46.4 wt. % of hydrophilic substances, including 9 to 25 wt. % of trimetazidinedihydrochloride; 52.2 to 54.0 wt. % of non-soluble substances, including 26.0 to 27.0 wt. % of a methacrylic acid polymer; and adjuvants. The invention also involved a trimetazidinedihydrochloride-containing medication in the form of a 24-hour extended-release matrix tablet containing: 33.0 to 34.7 wt. % of hydrophilic substances, including 13.6 to 16.7 wt. % of trimetazidinedihydrochloride; 52.2 to 54.0 wt. % of non-soluble substances, including 26.0 to 27.0 wt. % of a methacrylic acid polymer; and adjuvant. The invention also relates to methods for producing said trimetazidinedihydrochloride-containing medication in the form of a 12-hour or 24-hour extended-release matrix tablet<sup>5</sup>. Amidon GE, *et al* 2010, 2008 formulate a sustained - release pharmaceutical composition in a form of an orally deliverable tablet comprising an active pharmaceutical agent having solubility not less than about 10 mg/ml, dispersed in a matrix comprising a hydrophilic polymer and a starch having a tensile strength of at least about 0.15 kNcm<sup>2</sup> at a solid fraction representative of the tablet<sup>6,7</sup>. Hardy I *et al* deal with the use of polyvinyl pyrrolidone (PVP) for the modulation of drug release kinetics from hydrophilic polymer matrix tablets, in particular hydroxyl propyl methyl cellulose (HPMC) matrix tablets. Another aspect of the invention is a method of drug release from a hydrophilic polymer matrix tablet, for example hydroxyl propyl methyl cellulose (HPMC) and compositions thereof<sup>8</sup>. Jain GK and Mukherji G, *et al* 2008, 2006 have patented hydrophilic matrix tablet which is suitable for the once-a-day administration of

valproate compounds such as divalproex sodium. The tablet comprises from about 10 weight percent to about 90 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; more than about 55 weight percent of a pharmaceutically acceptable hydrophilic polymer, from about 0.2 weight percent to about 9.5 weight percent of a lubricant, and from about 3 weight percent to about 15 weight percent of a filler; all weight percentages based upon the total weight of the tablet dosage form. Other aspects of the invention relate to the use of this formulation in the treatment of epilepsy and to methods for manufacturing this dosage form<sup>9,10</sup>.

### Solvent activated gel forming hydrophilic matrix system

The solvent activated matrix systems are a method to obtain zero order release, constant release over an extended period. Solvent activated delivery systems are a collective term comprising those systems in which the interaction between hydrophilic polymer and water is responsible for achieving controlled release. The interaction with water may include swelling, dissolution or degradation of the polymer. Gel forming hydrophilic matrix tablet is the type of solvent activated matrix system.

### Gel forming hydrophilic matrix system

Gel forming hydrophilic/swell able systems is homogenous or heterogenous systems in which the drug is dispersed in a swell able/hydrophilic polymer (see in Figure 2). These systems offer the possibility to obtain a constant drug delivery over an extended period of time. Upon swallowing gel forming matrix tablets, polymer is plasticized by the aqueous gastro-intestinal fluid due to which it undergoes macromolecular chain relaxation and volume expansion. Drug release is controlled by diffusion of the dissolved drug through the swollen gel-layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlled gel<sup>11</sup>.

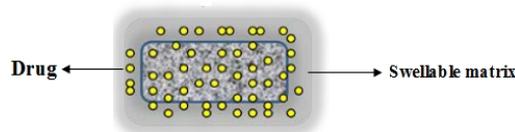


Figure 2: Gel Forming Hydrophilic Matrix System<sup>12</sup>

Jain G, *et al* 2007 have invented a sustained release solid pharmaceutical composition comprising antihypertensive, in particular, Metoprolol succinate or pharmaceutically acceptable derivatives thereof and a process for preparing such a formulation. The present invention is a composition comprising Metoprolol succinate or its pharmaceutically acceptable derivatives thereof and the composition releases the drug over 24 hours. The composition further comprises hydrophilic polymer matrix based tablets. The present invention describes a sustained release tablet comprising sustained release matrix comprising of gelling agents comprising at least one hydrophilic polymer with one or more gum and gum derivatives<sup>13</sup>. Katzhendler I, *et al* 1998 deals with a zero-order sustained-release delivery system for delivery of carbamazepine. A matrix tablet formulations of carbamazepine comprising hydrophilic polymer gel which inhibits transformation of carbamazepine into carbamazepine di-hydrate by causing morphologic changes of carbamazepine crystals and results in amorphous form of carbamazepine present in the polymer matrix<sup>14</sup>.

### Fat-Wax Matrix System

In this system drug can be dispersed into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminute for controlled-release granulations. The mixture of active ingredients, waxy materials and fillers can be converted into granules by compacting with roller compactor, heat this mixture in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes and is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GIT. The addition of surfactants into the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix<sup>15</sup>. Salama P, *et al* 2011 have developed a suspension which comprises an admixture in solid form of a therapeutically effective amount of a therapeutic agent (such as Cholecystokinin, octreotide), at least one salt of a medium chain fatty acid, a matrix forming polymer and a hydrophobic (lipophilic) medium. A surfactant may be included in the suspension. The pharmaceutical compositions may be formulated in a capsule or tablet for oral delivery<sup>16</sup>. Rajesh K, *et al* 2011 have invented to an extended release pharmaceutical composition such as tablets and capsules, and in particular to a matrix tablet composition comprising a therapeutically effective quantity of Tolterodine or pharmaceutical acceptable salts thereof incorporated in a hydrophobic matrix comprising water insoluble polymer and wax and a method for the preparation thereof<sup>17</sup>. Jang CG, *et al* 1984 involves a hydrophobic carbohydrate polymer, e.g. ethyl cellulose; and, generally at least one digestive-difficulty soluble component, i.e., a wax, e.g. carnauba wax, fatty acid material or neutral lipid provides upon dry direct compression a controlled and continuous release matrix for tablets or implants of biologically active agents. Preferred for producing dry direct compressed products is the combination of: a hydrophobic cellulose derivative; a wax, and, a fatty acid material and/or a neutral lipid since it provides upon dry direct compression a controlled and continuous release tablet

or implant of improved structural integrity against externally imposed forces<sup>18</sup>.

### Plastic Matrix (Hydrophobic) System

In this system of obtaining sustained release from an oral dosage form, drug is dispersed in an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compressed polymer particles. This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used (as shown in Figure 3). The primary rate-controlling mechanism of hydrophobic matrix is water insoluble in nature. Examples of materials that have been used as inert or hydrophobic matrix include waxes, polyethylene, glycerides, and polyvinyl chloride<sup>2</sup>. To modulate drug release, it may be necessary to incorporate soluble ingredients into formulation such as lactose. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism<sup>19</sup>.



Figure 3: Hydrophobic Matrix System

Federico S, *et al* (2011) have developed controlled release tablets containing glucosamine and a hydrophobic matrix and tablets prepared with wet granulation, hot granulation<sup>20</sup>. Dudhara KM, Mungre AP 2003 relates with invention that comprises carbamazepine and one or more hydrophobic polymers in the homogenous admixture, wherein the system does not comprises any means capable of preventing the conversion of carbamazepine to its dehydrate form. The present invention provides an oral controlled drug delivery of carbamazepine, which system is simple, uncomplicated and easy to manufacture<sup>21</sup>.

### Bio-Degradable Matrix System

Bio-degradable matrix systems consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded by enzymes which are generated by surrounding 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 aliphatic poly (esters) and poly anhydrides<sup>22</sup>. Thomas F, *et al* 2011 has patented an extended release tablet formulation in which pramipexole or a pharmaceutically acceptable salt thereof is included in a matrix including at least two water-swelling polymers. One of the polymers is gelatinized starch and the other is an anionic polymer<sup>23</sup>. Amidon GE, *et al* 2009 relates sustained-release composition comprises an active pharmaceutical agent having solubility not less than about 10 mg/ml, dispersed in a matrix comprising a hydrophilic polymer, a starch having a tensile strength of at least about 0.15 kNcm<sup>2</sup>

at a solid fraction representative of the tablet, wherein the compatibility of the starch is determined in the method estimating the tensile strength<sup>24</sup>. Himadri S, *et al* 2002 have patented a tablet for controlled release of an active ingredient comprises a beta lactam antibiotic such as cephalexin, cefaclor or their pharmaceutically acceptable hydrates, salts or esters as active ingredient, and a mixture of hydrophilic polymers selected from the group consisting of at least one sodium alginate and at least one xanthan gum as controlled release matrix; and optionally probenecid as an antibiotic adjuvant as either immediate release or controlled release part. The composition may also contain one or more of a water soluble and/or water dispersible diluent, wherein the quantities of the hydrophilic polymer matrix but still provides the desired once a day profile. The resulting modified release matrix formulation not containing probenecid may be administered once or twice daily. The resulting modified release matrix formulation containing probenecid may be administered once daily<sup>25</sup>.

#### Mineral Matrix System

These systems 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 (Phaeophyceae) by the use of dilute alkali<sup>15</sup>. Jain GK, *et al* 2004 deals with extended release matrix tablets for oral administration that include a cationic polymer, x such a methacrylic acid derivative with a dimethyl-amino-ethyl ammonium group such as a water-swallowable cellulose derivative and an alginic acid derivative to cause the release rate of the active ingredient of the tablets to be independent of pH and gastric residence time. The present invention also relates to a dual release matrix tablet of carvedilol. The pharmaceutical composition includes carvedilol formulated into an extended release core wherein a portion of the core is surrounded by a second immediate release layer of carvedilol<sup>26</sup>.

#### Matrix System Based on Porosity

Development of porous matrix is useful for stable uniform porous structure, tunable pore size high surface area, and well-defined surface properties. Various types of pores like open, closed, transport and blind pores in the porous matrix system allow them to adsorb drugs and release them in a more reproducible and predictable manner. Pharmaceutically exploited porous adsorbents includes, ethylene vinyl acetate (macro-porous), silica (meso-porous), polypropylene foam powder (micro-porous), titanium dioxide (nano-porous). When porous polymeric drug delivery system is placed in contact with appropriate dissolution medium, release of drug to medium must be preceded by the drug dissolution in the water filled pores or from surface and by diffusion through the water filled channels<sup>27</sup>.

#### Macro Porous Systems

In such systems, the diffusion of drug occurs through pores of matrix system, which have size range 0.1 to 1  $\mu\text{m}$ . This pore size is larger than diffusant molecule size.

#### Microporous System

Diffusion in this type of system occurs essentially through pores of matrix. For micro-porous systems, pore size ranges between 50-200  $\text{\AA}$ , which is slightly larger than diffusant molecules size.

#### Non-Porous System

Non-porous systems have no pores and drug diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present<sup>15</sup>.

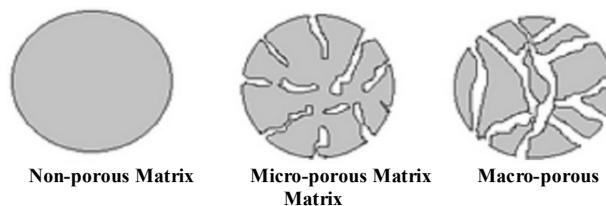


Figure 4: Porous Matrix System<sup>28</sup>

Pavuluri VR, *et al* 2002 relates with a novel freeze - dried pharmaceutical composition useful for the treatment of migraine and associated symptoms at a reduced total dose of active substance than required for oral administration in the form of a tablet containing a porous matrix network of a water soluble or water dispersible carrier material, a pharmaceutically active substance(s); organoleptic additives such as sweetening agents, flavoring agents, coloring agents; pharmaceutically acceptable preservatives; solubilizing agents; surface-active agents and/or buffering agents. The pharmaceutical composition optionally may contain other additives such as permeation enhancers, chelating salts and stabilizing agents<sup>29</sup>. Allen LV, *et al* 1995 have developed a support matrix, a solid dosage form made there from, and processes for making such support matrices and dosage forms, which disintegrate or dissolve in a matter of just a few seconds once placed into the oral cavity. First, a porous particulate powder which will serve as the tablet support matrix is produced. In the second step, the pharmaceutical, for example an antihistamine, decongestant, or antibiotic is combined with the powder. Other additives may also be added to the mixture. In the third step the mixture is formed into a tablet. Finally, in the fourth step, a coating may be applied to the outer surface of the tablet to enhance the intactness and durability of the tablet<sup>30</sup>. Bosmans E, *et al* 1986 have patented immune-sorbent usable in immunologic determinations based on a porous matrix of poly-tetra-fluoro-ethylene wherein there is covalently bound an organic or inorganic, hydrophilic or hydrophobic, water-insoluble polymer, to which are covalently associated antigens and/or antibodies in well determined amounts and, if there are various antigens and/or antibodies, in well determined proportions. The method for the preparation of such an immune-sorbent comprises the following steps: the insoluble porous polymer, activated, non-activated or coupled by the antigen or antibody is mixed together with the porous base matrix in a pulverulent state to form a dry mixture, the dry mixture is subjected to an agglomeration treatment to form agglomerates, the agglomerates thus formed are subjected to a crushing treatment to form crushed agglomerates, the crushed agglomerates are compressed together to form a compressed tablet and the tablet is subjected to a rolling or laminating process to obtain a film or a sheet<sup>31</sup>.

#### Miscellaneous

##### Multilayered Matrix System

A new multi-layer matrix tablet design has recently been proposed for constant drug release. Multilayered tablets, for controlled release usually consist of a drug core layer which

is sandwiched by external layers. These layers may contain dissimilar amounts of drug to form a concentration gradient matrix or just act as a barrier layer in Figure 5. Multilayered matrix devices are based firstly on the matrix hydration rate and subsequent swelling and/or lowering of diffusion rate and secondly modulation of the surface of matrix through which the drug can be delivered. Main advantage of this system is to avoid dose dumping<sup>32</sup>.

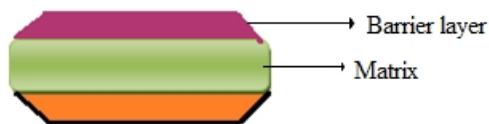


Figure 5: Multilayered matrix system

Kohlrauseh A, *et al* 2006, 2005 have patented multilayer tablet that comprises a first layer formulated for instant release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix, a second layer formulated for instant release of the angiotensin converting enzyme inhibitor ramipril and optionally a diuretic from a disintegrating tablet matrix, and, optionally, a third layer formulated for instant release of a diuretic like hydrochlorothiazide from a fast disintegrating tablet matrix<sup>33,34</sup>. Olivier S, *et al* 2000 have developed a multilayer tablet for the instant and then prolonged release of active substances comprising at least two superposed layers, characterized in that: a first outer layer is composed of a mixture of excipients and of a first active substance, the said first layer allowing immediate release of the said first active substance; a second layer, arranged in contact with the said first layer, consists of a non-biodegradable, inert porous polymeric matrix in which a second active substance is dispersed<sup>35</sup>.

### Floating Matrix System

The principle of these systems offers a simple and practical approach to achieve increased gastric residence time and sustained drug release for the dosage form. These systems develop by melt granulation technique that generates CO<sub>2</sub>. This reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at the desired rate. These systems are designed to retain drug in the stomach for longer period of time, and hence significantly prolong the gastric residence time of drugs in Figure 6<sup>36</sup>.

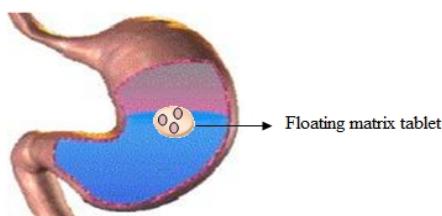


Figure 6: Floating matrix system

Maheswari D, *et al* 2006 have invented a process for the preparation of controlled release gastric floating matrix oral dosage form of Imatinib or its pharmaceutically acceptable salts and its polymorphs such as  $\beta$  and  $\alpha$ ; 2, Form I and Form 2 thereof for once daily administration in the form of coated tablet or mini-tablets and / or pellets filled in hard gelatin capsules<sup>37</sup>. Tuliani V, Brandley MA 2006 have

developed a pharmaceutical composition in the form of a tablet comprising an effective amount of Compound A, a swelling polymer, a matrix polymer, a floating agent, and optionally further comprising a diluent, a binder, a glidant, and / or a lubricant. Also disclosed is a method of treating or preventing thromboembolic disorders comprising administering an effective amount of the composition to a patient in need thereof<sup>38</sup>.

### pH Sensitive Matrix System

These are intestine and colon targeted delivery system with sustained release. In this system enteric coating provide the protection of the tablet matrix from acidic environment of the stomach by employing pH sensitive polymer, which swell or solubilize in response to an increase in pH to release the drug as shown in Figure 7<sup>39</sup>.

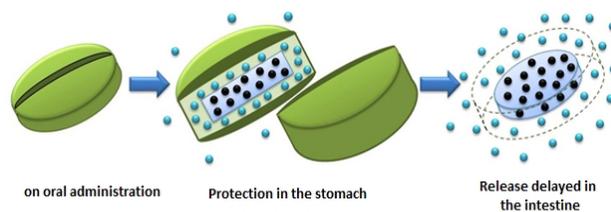


Figure 7: Enteric coated matrix system

Devid LB *et al* 2012 have patented an oral pharmaceutical tablet for controlled release of mesalazine or a pharmaceutically acceptable salt thereof as active ingredient with a core and a gastro-resistant outer coating, wherein the core comprises mesalazine and a hydrophilic matrix consisting of a mixture of hydroxyl-propyl-methyl cellulose (HPMC) having a different viscosity and the gastro-resistant outer coating comprises a pH-dependent release polymer, with the pharmaceutically acceptable excipients. The invention also refers to the process for obtaining said oral pharmaceutical tablet and oral pharmaceutical tablet of controlled release of mesalazine for treating ulcerative colitis<sup>40</sup>. Odidi I, Odidi A, 1998 have invented a pharmaceutically active substances that have a water contact angle ( $\theta(u)$ ) such that  $\cos \theta(u)$  is between + 0.9848 and - 0.9848 presented as a matrix tablet containing the said pharmaceutically active substances, with/without suitable pharmaceutical excipients in intimate mixture with two groups of intelligent polymers having opposing wettability characteristics, one demonstrating a stronger tendency towards hydrophobicity and the other a stronger tendency towards hydrophilicity, the polymer combination being between the ratios of 1:50 and 50:1 amounts effective to control the release of said pharmaceutically active substances in a mathematically predictable manner, wherein the polymer demonstrating a stronger tendency towards hydrophobicity is not less than 5 % wt/wt and preferably between 5-70 % wt/wt of the final formulation composition. The polymers have ethyl cellulose as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and/or hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic (the ratio of HEC to HPMC being between 1:100 and 100:1). The matrix tablet is optionally coated with an enteric coat, 0-5 % - 15 % wt/wt to prevent the initial burst effect seen in such systems and to impart gastrointestinal tract (GIT) 'stealth' characteristics especially in the presence of food<sup>41</sup>.

### Bio mucoadhesive Matrix System

Mucoadhesive sustained matrix system offer several advantages over other simple matrix tablet systems since they provide a sustained drug release over time, and target and localize the dosage form to a specific site. Mucoadhesive drug delivery devices can be applied to any mucosal tissue in the body, including the ocular, respiratory, gastrointestinal, buccal, nasal, rectal, urethral and vaginal path as in Figure 8. Since the GI tract is covered by a mucus layer, localization of a mucoadhesive drug delivery system to a specific site is very beneficial in mucous infection<sup>42</sup>. Bio mucoadhesive excipients are generally highly swellable hydrophilic polymers, which interact with the glycoproteins in the mucous layer<sup>42</sup>.

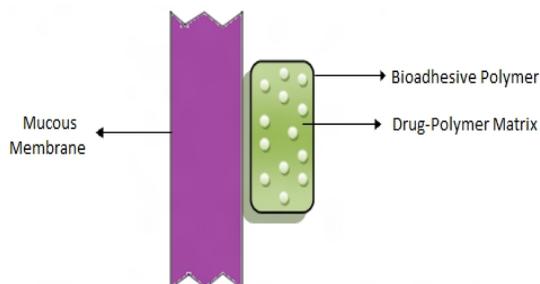


Figure 8: Mucoadhesive matrix system

Mathiowitz E, *et al* 2007, 2006 patented for selective, high efficacy delivery to specific regions of the mouth and gastrointestinal tract. The formulation is typically in the form of a tablet or capsule, which may include micro-particles or beads. The formulation uses bio-adhesive and controlled release elements to direct release to specific regions, where the drug is absorbed in enhanced amounts relative to the formulation in the absence of the bio-adhesive and/or controlled release elements. This is demonstrated by an example showing delivery of gabapentin with a greater area under the curve (AUC) relative to the FDA reference immediate release drug, i.e., the AUC of the composite bio-adhesive formulation is greater than 100 % of the AUC of the immediate release drug. In the preferred embodiments, the

formulation includes drug to be delivered, controlled release elements, and one or more bio-adhesive elements. The bio-adhesive polymer may be either dispersed in the matrix of the tablet or applied as a direct compressed coating to the solid oral dosage form. The controlled release elements are selected to determine the site of release. The bio-adhesive components are selected to provide retention of the formulation at the desired site of uptake and administration. By selecting for both release and retention at a specific site, typically based on time of transit through the gastrointestinal tract, one obtains enhanced efficacy of uptake of the drug. This is particularly useful for drugs with narrow windows of absorption, and drugs with poor solubility such as the BCE class III and class IV drugs<sup>43,44</sup>. Jacob JS, *et al* 2006, 2005 relates with Class II drugs that have low oral bioavailability due to their insolubility in water and slow dissolution kinetics and method for making such a drug delivery system are disclosed herein. The formulation may be a controlled release or immediate release formulation. The immediate release formulation contains a Class II drug, together with a hydrophobic polymer, preferably a bio-adhesive polymer. In one embodiment, the drug and polymer are co-dissolved in a common solvent. The solution is formed into small solid particles by any convenient method, particularly by spray drying. The resulting particles contain drug dispersed as small particles in a polymeric matrix. The particles are stable against aggregation, and can be put into capsules or tablet for administration. The controlled release formulations contain a BCS Class II drug and a bio-adhesive polymer. The controlled release formulations may be in the form of a tablet, capsules, mini-tab, micro-particulate, or osmotic pump. Enhancement of oral uptake of the drug from use of bio-adhesive polymers occurs through (1) increased dissolution kinetics due to stable micronization of the drug, (2) rapid release of the drug from the polymer in the GI tract; and (3) prolonged GI transit due to bio-adhesive properties of the polymers. The combination of these effects allows the preparation of a compact, stable dosage form suitable for oral administration of many class II drugs<sup>45,46</sup>. The patents across the globe in the field of oral controlled release pharmaceutical matrix system are compiled in Table 1.

Table 1: Patented Matrix System

S. No.	Patent No.	Title	Type of Matrix	Inventor, Year
1	EP2468264 and WO/2012/089677	Oral pharmaceutical tablet for controlled release of mesalazine and process for obtaining it	pH sensitive	LB Devid, <i>et al</i> (2012) <sup>40</sup>
2	WO/2011/008183	Trimetazidinedihydrochloride- containing medication in the form of an extended-release matrix tablet (variants) and methods for preparing same (variants)	Hydrophilic	RN Prykhodko, <i>et al</i> (2011) <sup>5</sup>
3	WO/2011/116139	Improved pharmaceutical compositions comprising Cholecystokinin and methods of delivery	Fat-wax	P. Salama, <i>et al</i> (2011) <sup>16</sup>
4	WO/2011/061616	Extended release compositions containing tolterodine and process for preparing the same	Fat-wax	K. Rajesh K, <i>et al</i> (2011) <sup>17</sup>
5	WO/2011/157730	Process for the preparation of controlled release tablet	Hydrophobic	S. Federico, <i>et al</i> (2011) <sup>20</sup>
6	JP2011/084577	Extended release tablet formulation containing pramipexole or pharmaceutically acceptable salt thereof, method for manufacturing the same and use thereof	Bio-degradable	F. Thomas (2011) <sup>23</sup>
7	EP2172199	Sustained release tablet comprising pramipexole	Hydrophilic	GE Amidon, <i>et al</i> (2010) <sup>6</sup>
8	JP2009185051	Sustained-release tablet comprising reboxetine	Bio-degradable	GE Amidon, <i>et al</i> (2009) <sup>24</sup>
9	WO/2008/004001	The use of PVP to control the release profile of an active ingredient from a hydrophilic polymer matrix tablet	Hydrophilic	Hardy, <i>et al</i> (2008) <sup>8</sup>
10	WO/2008/001151	Controlled release compositions of divalproex sodium	Hydrophilic	G. Jain, <i>et al</i> (2008) <sup>9</sup>
11	EP1987832	Sustained release tablet comprising pramipexole	Hydrophilic	GE Amidon, <i>et al</i> (2008) <sup>7</sup>
12	WO/2007/029070	Extended release composition of metoprolol succinate	Hydrophilic gel forming	G. Jain, <i>et al</i> (2007) <sup>13</sup>
13	EP1789024	Controlled regional oral delivery	Biomucoadhesive	E. Mathiowitz, <i>et al</i> (2007) <sup>43</sup>
14	WO/2006/039022	Controlled regional oral delivery	Biomucoadhesive	E. Mathiowitz, <i>et al</i> (2006) <sup>44</sup>

15	EP1729741	Polymeric drug delivery system for hydrophobic drugs	Biomucoadhesive	JS Jacob, <i>et al</i> (2006) <sup>45</sup>
16	WO/2006/089215	Pharmaceutical compositions and methods	Floating matrix	V. Tuliani, MA Brandley (2006) <sup>38</sup>
17	WO/2006/040779	Controlled release gastric floating matrix formulation containing imatinib	Floating matrix	D. Maheswari, <i>et al</i> (2006) <sup>37</sup>
18	WO/2006/064321	Controlled release compositions of divalproex sodium	Hydrophilic	G. Mukhrji, <i>et al</i> (2006) <sup>10</sup>
19	WO/2005/084639	Polymeric drug delivery system for hydrophobic drugs	Biomucoadhesive	JS Jacob, <i>et al</i> (2005) <sup>46</sup>
20	US20050186274 A1	Multilayer tablet	Multilayer tablet	A. Kohlrausch, <i>et al</i> (2005) <sup>34</sup>
21	EP1718281 A1	Multilayer tablet	Multilayer tablet	A. Kohlrausch, <i>et al</i> (2006) <sup>33</sup>
22	WO/2004/096182	Extended release matrix tablets of carvedilol	Mineral	GK. Jain, <i>et al</i> (2004) <sup>26</sup>
23	US2003/0175353	Oral controlled drug delivery system	Hydrophobic	KM Dudhara, AP Mungre, <i>et al</i> (2003) <sup>21</sup>
24	EP1246668	Composition pharmaceutique lyophilisee a action rapide s'administrant par voie orale utilisee pour traiter la migraine	Porous	VR Pavuluri, <i>et al</i> (2002) <sup>29</sup>
25	WO/2002/041876	Pharmaceutical composition for controlled release of an active ingredient	Bio-degradable	S. Himadri, <i>et al</i> (2002) <sup>25</sup>
26	US5,980,942	Zero-order sustained release matrix tablet formulations of carbamazepine	Hydrophilic gel forming	I. Katzhendler, <i>et al</i> (1998) <sup>14</sup>
27	WO/1998/047491	Controlled release formulations using intelligent polymers	pH sensitive	I. Odidi, A. Odidi, <i>et al</i> (1998) <sup>41</sup>
28	WO/1995/020377	Rapidly dissolving oral dosage form	Porous matrix	Allen, V. Loyd, <i>et al</i> (1995) <sup>30</sup>
29	WO/1986/006491	Immuno active components immobilized in a porous material	Porous matrix	E. Bosmans, <i>et al</i> (1986) <sup>31</sup>
30	WO/1984/004674	Dry direct compression compositions for controlled release dosage forms	Fat-wax matrix	CG Jang, <i>et al</i> (1984) <sup>18</sup>

## CONCLUSION

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages and disadvantages, various polymers used to design such system and various patents in the field of matrix system. Above discussion, it can be easily concluded that controlled-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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