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# Pharmaceutical Controlled Release Drug Delivery Systems: A Patent Overview

**Sahilhusen I Jethara[1, 2]*, Mukesh R Patel[2]**

[1]Research scholar, Gujarat Technological University, Gujarat, India

[2]Shri B. M. Shah College of Pharmaceutical Education & Research, Modasa-383315, Gujarat, India

**Abstract**

Controlled drug delivery system is to make sure safety and to improve effectiveness of the drugs as well as patient compliance. A controlled release system includes any delivery system that achieves slow release of the drug over an extended period of time. This is achieved by better control of plasma drug level and less frequent dosing. Successful commercialization of a controlled release formulation is frequently challenging and involves consideration of many factors such as physiochemical properties of the drug, physiological factors, and manufacturing variables. The rationalization for the development of controlled release drug delivery system of a drug is to improve its therapeutic benefits, minimizing its side effects even as improving the management of the diseased condition. It is the purpose of this piece of writing to comprehensively review drug delivery system design for control release by discussing the recent patents available.

**Abbreviations:** CR: Controlled Release; SR: Sustained Release; PVP: Poly Vinyl Pyrrolidone; EC: Ethyl Cellulose; HPMC: Hydroxypropylmethyl Cellulose; US: United States Patent; CN: China Patent; WO: World Intellectual Property Organization (WIPO); EP: European Patent; KR: South Korea Patent; CA: Canadian Patent; JP: Japan Patent; MX: Maxico Patent; NZ: New Zealand Patent; AU: Australian Patent; TW: Taiwan Patent

**Keywords**: Controlled release drug delivery; Dose; Patents; Pharmaceuticals drug delivery; Patient compliance; Sustained Release (SR) system

***Correspondence Author**: Sahilhusen I Jethara, Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education and Research, College Campus, Modasa -383315, Gujarat, India; Tel: +918460378336; E-mail: sahil.pharm4@gmail.com

## Introduction

Over the past decades, as the expenditure and complications occupied in advertising novel drug entities have augmented, with related recognition of the therapeutic compensation of controlled drug-delivery, superior consideration has been focused on enlargement of sustained- or controlled-release drug delivery systems. Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. A perfect controlled drug delivery system is the one which deliver the drug at a pre-determined rate, locally or systemically, for a precise period of time. Different conventional immediate release system, the rate of appearance of drug in the body among such a system is not controlled by

absorption process. The enthusiasm designed for controlled drug release is necessary to uphold the secure effective drug concentration in the body for an extended time period. For most favorable performance, drug concentration in the body should be maintained on top of the effective level and under the toxic level. Yet when drug is administered to a patient, the initial concentration of the drug in the body is above a toxic level before regularly diminished to an ineffective level due to excretion. Dilution of the drug in the body fluid will be impend absorption by tissue and transport in the bloodstream. A peaceful drug delivery system should deliver the drug at the rate dictated by the requirements of the body over the period of treatment i.e. it should provide the desired therapeutic concentration of drug in the plasma and maintain it constant for the entire duration of treatment. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist the effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained- or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. If one were to imagine the ideal drug delivery system, two fundamentals would be compulsory. First, it would be a single dose for the duration of treatment, whether it is for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should carry the active entity directly to the site of action, thus minimizing or eliminating side effects. This may require delivery to specific receptors or to localization to cells or to specific areas of the body. It is obvious that this fantasy delivery system will include changing requirements for different disease states and different drugs. Therefore we wish to deliver the therapeutic agent to a specific site for a specific time. In other words, the objective is to achieve both spatial and temporal placement of drug. Currently, it is possible to only partially achieve both of these goals with most drug-delivery systems [1, 2].

Polymers have been productively working in the formulation of solid, liquid and semi-solid dosage forms and are exclusively useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose. But the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible of increasing consequence is the fact that plant resources are renewable and if refined or harvested in a sustainable way, they can offer a constant supply of raw material. By tradition, excipients were incorporated in drug formulations as inert vehicles that provided the needed weight, consistency and volume for the accurate administration of the active ingredient, but in modern pharmaceutical dosage forms they often fulfill multi-functional role such as improvement of the stability, release and bioavailability of the active ingredient, enhancement of patient tolerability and performance of technological functions that ensure ease of manufacture [3, 4].

In recent years, in association with advancement and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop sustained release dosage forms for many drugs. Pharmacokinetic theory suggests that the ultimate method for reducing the plasma maximum concentration ($C_{max}$) to plasma minimum concentration ($C_{min}$) ratio is to have zero-order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists. Successful commercialization of an extended release formulation is usually challenging and involves consideration of many factors such as physiochemical properties of the drug, physiological factors, and manufacturing variables [5].

**Figure: 1**

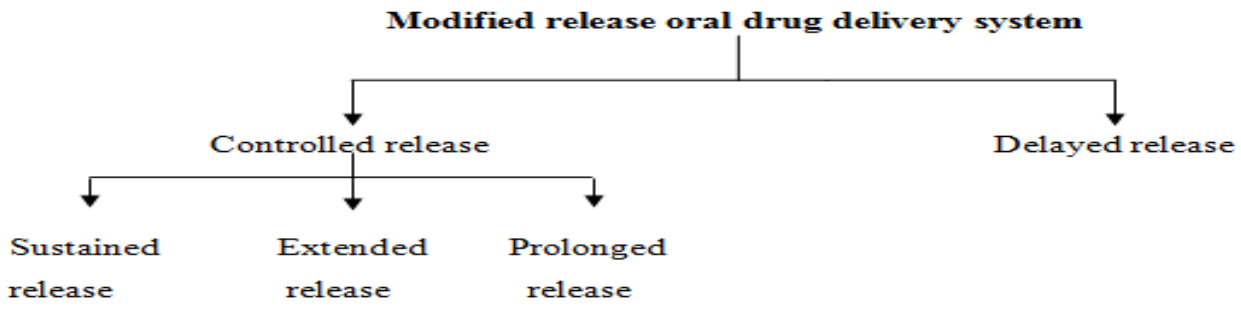


**Figure 1:** Modified release oral drug delivery systems

## 1. Classification of Controlled Release Drug Delivery Systems [6-8]

Depending upon the mode of drug release, these systems are classified as follows;

### 1.1. Diffusion systems

Two types of diffusion system are reservoir devices and matrix devices.

Three types of diffusion matrix system are hydrophobic, hydrophilic and fat-wax matrix system.

### 1.2. Dissolution sustained systems

Dissolution sustained systems are soluble reservoir, soluble matrix and dissolution- sustained pulsed delivery system.

### 1.3. Methods using osmotic pressure

- Single chamber osmotic pump
  - Elementary Osmotic Pump(EOP)
- Multi chamber osmotic pump
  - Push pull osmotic pump.
  - Osmotic pump with non expanding second chamger
- Specific types

  Most widely used different specific type's osmotic systems are; controlled porosity osmotic pump, monolithic osmotic systems, osmotic bursting osmotic pump, OROS-CT, Multi-Particulate Delayed Release Systems (MPDRS) and Liquid Oral Osmotic System (L-OROS).

### 1.4. Altered density formulations

### 1.5. Swelling and expansion systems

### 1.6. Ion exchange resins systems

### 1.7. Mineral Matrix system based on porosity

Mineral matrix based on porosity systems such as macro porous, micro porous and non-porous system.

### 1.8. Miscellaneous Matrix system

Miscellaneous matrix systems are bio-mucoadhesive, floating, pH sensitive formulations and biodegradable

## 2. Patented Pharmaceutical Controlled Release System

The present overview places of interest a good number pioneering controlled or sustained release technology derived from modern patents and also provide a outline of various patented controlled release technology platform. The international databases of Patent Analysis Software CobaltIP 2012, Freepatentonline, Patentlense, WIPO, Patents Scope, United States Patent Office (USPTO) and Google patent were employed to collect the patents and the patent applications.

**Figure 2:** Schematic representation of (1) Prototype matrix system, (2) Gel forming hydrophilic matrix system, (3) Hydrophobic matrix system, (4) Porous matrix system, (5) Enteric coated matrix system, (6) Floating matrix system, (7) Mucoadhesive matrix system, (8) Multilayered matrix system and (9) Diffusion release pattern.

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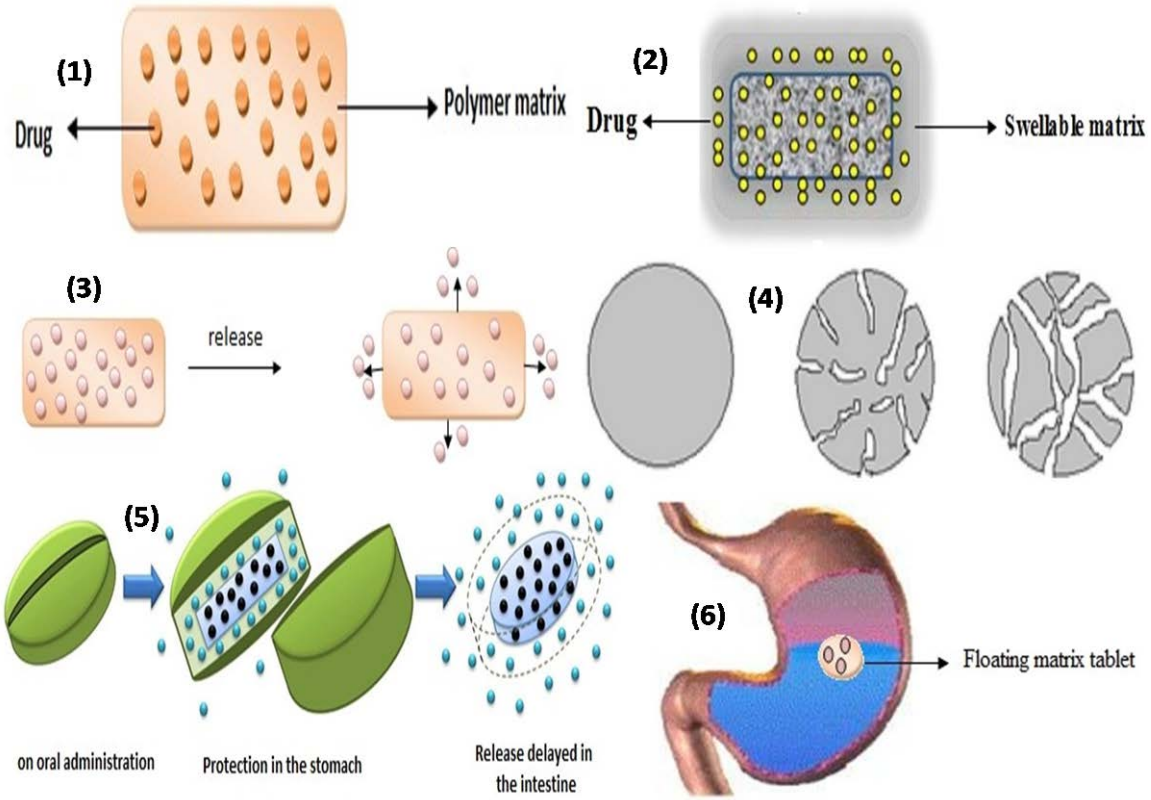


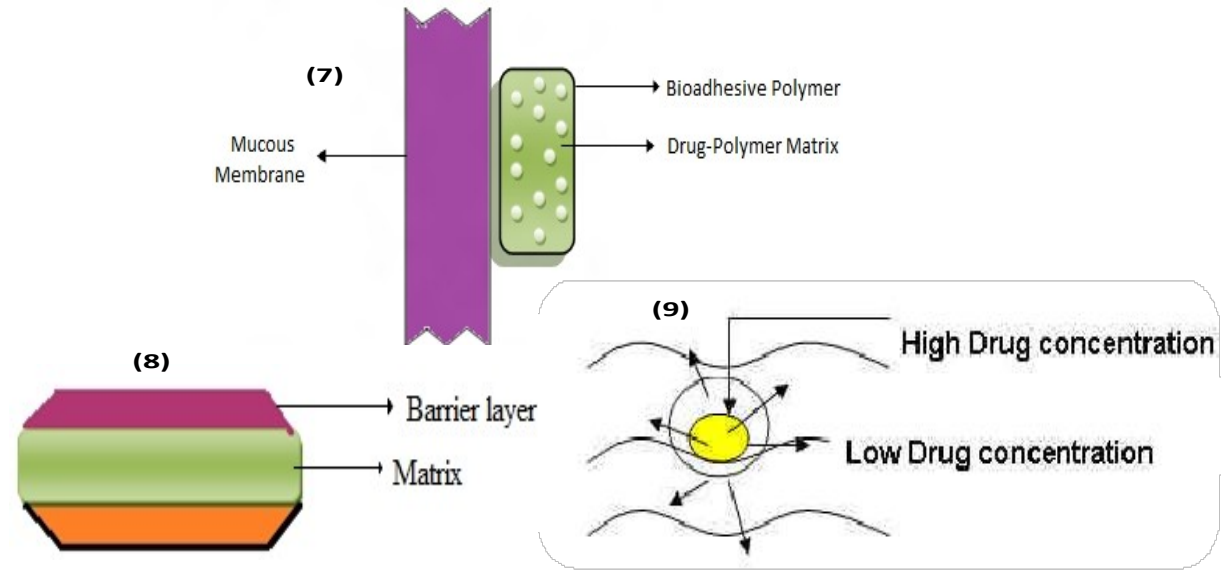

**Table 1:** Patented controlled release drug delivery systems

| Title | Patent number | Inventor | Year | Ref. |
|---|---|---|---|---|
| **1. Biodegradable Controlled Release Systems** | | | | |
| Multiblock biodegradable hydrogels for use as controlled release agents for drugs delivery and tissue treatment agents | WO/1997/005185 | Pathak CP et al. | 1997 | [9] |
| Multiblock biodegradable hydrogels for use as controlled release agents for drugs delivery and tissue treatment agents | MX9801706 | Bartusiak JT et al. | 1998 | [10] |
| Biodegradable polymer matrices for sustained delivery of anesthetics | US6214389, US6214388 | Lee H et al. | 1999<br>2000 | [11]<br>[12] |
| Biodegradable polymer matrices for sustained delivery of local anesthetic agents | US6214387 | Berde CB et al. | 2001 | [13] |
| Controlled release formulation | JP2000239104 | Sadamoto M et al. | 2002 | [14] |
| Biodegradable controlled release bioactive agent delivery device | US20060034891, WO/2006/023130 | Lawin L et al. | 2006 | [15, 16] |
| Controlled release formulations | US20090110735 | Maggio ET et al. | 2009 | [17] |
| Baclofen and r-baclofen gastroretentive drug delivery systems | US20110091542 A1 | Navon N et al. | 2011 | [18] |
| Method for preparation of controlled release formulations | JP2011144207 | Gary CP | 2011 | [19] |
| Intrauterine sustained control release drug delivery system adopting biodegradation material, and preparation method thereof | CN102743328 | Jianxin L et al. | 2012 | [20] |
| **2. Biomucoadhesive Controlled Release Systems** | | | | |
| A biocompatible adhesive system and a bioadhesive drug delivery system with controllable release | WO/2000/047644, AU2547900 | Remon JP et al. | 2000 | [21, 22] |
| Controlled regional oral delivery | WO/2006/039022 | Mathiowitz E et al. | 2006 | [23] |
| Controlled release oral delivery systems | EP2484223 | Gebreselassie P et al. | 2012 | [24] |
| **3. Floating Controlled Release Systems** | | | | |
| Floating oral formulations for controlled release of betaine | WO/2004/091601, EP1615632 | Messadek J | 2004<br>2006 | [25]<br>[26] |
| Controlled release gastric floating matrix | WO/2006/040779 | Parvataneni DM et al. | 2006 | [27] |

| | | | | |
|---|---|---|---|---|
| formulation containing imatinib | | | | |
| Colchicines gastric floating sustained-release tablet and method for preparing same | CN101536990 | Wenping W et al. | 2009 | [28] |
| Metformin hydrochloride intragastric floating sustained-release tablet and preparation method thereof | CN101536989 | Wanqing W et al. | 2009 | [29] |
| Intra-gastric floating sustained-release tablets containing floating konjac glucomannan and preparation method thereof | CN102258494 | Deng Y et al. | 2012 | [30] |
| Method for preparing xanthan gum omeprazole intragastric retention floating sustained-release tablets | CN102552202 | Ruiyan Z et al. | 2012 | [31] |
| Ranitidine bismuth citrate intra-gastric floating sustained-release tablet and preparation method thereof | CN103054828 | Lv M et al. | 2013 | [32] |
| Preparation of xanthan gum vildagliptin intragastric retentive floating sustained-release tablet | CN102846567 | Zhan R et al. | 2013 | [33] |
| Intra-gastric floating type cuttlebone sustained release tablet for treating gastric ulcer and preparation method thereof | CN103479674 | Zhang A et al. | 2014 | [34] |
| **4. Osmotically Controlled Release Systems** | | | | |
| Osmotic controlled release drug delivery device | CA2388159 | Ruddy SB et al. | 2001 | [35] |
| | AU1444301 | | 2001 | [36] |
| | WO/2001/032149 | | 2001 | [37] |
| | EP1227800 | | 2002 | [38] |
| Floating osmotic device for controlled release drug delivery | US20030064101 | Mehta BP et al. | 2003 | [39] |
| Oral osmotic controlled drug delivery system | WO/2003/096968 | Dharmadhikari NB et al. | 2003 | [40] |
| Potassium chloride elementary osmotic pump controlled release tablet and preparation method thereof | CN102144985 | Yihua W et al. | 2011 | [41] |
| **5. Multilayer Controlled Release Tablets** | | | | |
| Multilayer tablet | US6254886 | Fusca M et al. | 2001 | [42] |
| Multilayer tablet | WO/2005/079762 A1, US20050186274 A1 | Kohlrausch A | 2005 | [43, 44] |

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|---|---|---|---|---|
| Multilayer omeprazole tablets | US20090280173 A1 | Chauhan I et al. | 2009 | [45] |
| Multilayer tablet | US20140065217 A1 | Zerbe HG et al. | 2014 | [46] |
| **6. Diffusion Matrix System [Hydrophobic, Hydrophilic and Fat-wax - Matrix System]** | | | | |
| Sustained release carbamazepine formulation | EP1044681 A2 | Licht D et al. | 2000 | [47] |
| Sustained release formulation of carbamazepine | US6162466 | | | [48] |
| Controlled release and taste masking oral pharmaceutical compositions | WO/2000/076478 | Villa R et al. | 2000 | [49] |
| Mesalazine controlled release oral pharmaceutical compositions | WO/2000/076481 | Villa R et al. | 2000 | [50] |
| Control-release agrochemical formulation and its production | JP2000239105 | Kamata, Y et al. | 2002 | [51] |
| Oral drug delivery system | WO/2002/062314 | Tucker MR et al. | 2002 | [52] |
| Zero-order sustained release matrix tablet formulations of carbamazepine | US5980942 | Katzhendler I et al. | 1999 | [53] |
| Controlled-release formulation coated with aqueous dispersion of ethyl cellulose | JP2006188539, JP2006188540 | Oshlack B et al. | 2006 | [54] [55] |
| Sustained-release tablet composition | US20070196481 A1 | Amidon GE et al. | 2007 | [56] |
| Melt-processed imatinib dosage form | EP1920767 A1 | Breitenbach J et al. | 2008 | [57] |
| Controlled-release formulations | WO/2008/008434 | Nutalapati S et al. | 2008 | [58] |
| Sustained-release tablet composition | US20090143387 A1 | Amidon GE et al. | 2009 | [59] |
| Sustained release tablet comprising pramipexole | EP2172199 A1 | Amidon GE et al. | 2010 | [60] |
| Opioid formulation having extended controlled release | JP2009149681 | Sackler R et al. | 2009 | [61] |
| Controlled-release formulations | WO/2010/083360 | Arnold K et al. | 2010 | [62] |
| Controlled release formulation of octreotide | JP2010189401 | Kuzma P et al. | 2010 | [63] |
| Solid agrochemical formulation having controlled release of agrochemical active ingredient | JP2010168298 | Ogoshi A | 2010 | [64] |
| Extended-release pharmaceutical formulations | WO/2010/080580 | Cardinal JR et al. | 2010 | [65] |
| Improved formulation for controlled release of drugs by combining hydrophilic and hydrophobic agents | JP2011005300 | Kochinke F et al. | 2011 | [66] |
| Controlled release hydrogel formulation | US20110165236 | Chow S et al. | 2011 | [67] |
| Controlled release formulation containing vardenafil | JP2012254993 | Zuleger S et al. | 2012 | [68] |
| Imatinib formulations | WO/2013/008253 A2 | Konatham S et al. | 2013 | [69] |

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|---|---|---|---|---|
| **7. Mineral Matrix Based on Porosity [Macro, Micro and Non-porous system]** | | | | |
| Rapidly dissolving oral dosage form | WO/1995/020377 | Allen VJL et al. | 1995 | [70] |
| Controlled-release formulations | US20080095843 | Nutalapati SRK et al. | 2008 | [71] |
| Porous calcium phosphate bone material | US8147860 | Rosenberg AD et al. | 2012 | [72] |
| **8. Dissolution Sustained - Water Soluble Matrix System** | | | | |
| Medicine release-control type percutaneous absorptive formulation | JP09012448 | Mori M | 1997 | [73] |
| Sustained release caffeine formulation comprising microparticles have a biodegradable water soluble matrix that are uniformly distributed and to a method of making it | NZ295245 | Enslen MYA et al. | 1999 | [74] |
| Controlled release KCl tablet formulations | EP1244429 | Gantt M et al. | 2002 | [75] |
| Production of sustained release formulation of water soluble peptides containing polypeptide, preferably somatostatin or octreotide in polymeric matrix, preferably poly (lactide-co-glycolide) glucose | KR100442931 | Bodmer D et al. | 2004 | [76] |
| Controlled-release pharmaceutical formulations | US20040076668 | Berchielli A et al. | 2004 | [77] |
| Controlled-release pharmaceutical formulation | US20070141149 | Kuhar P et al. | 2007 | [78] |
| Controlled release pharmaceutical formulation | US20070224269 | Rubino OP et al. | 2007 | [79] |
| Controlled release pharmaceutical compositions | WO/2009/042778 | Mulye N | 2009 | [80] |
| Controlled release formulation | WO/2012/006961 | Zhong S | 2012 | [81] |
| **9. pH Sensitive Matrix Systems** | | | | |
| Controlled release formulation | WO/2007/052299<br>US20080248107 | Pilgaonkar PS et al. | 2007<br>2008 | [82]<br>[83] |
| Oral insulin delivery systems for controlling diabetes | WO/2010/113177 | Vidhya R et al. | 2010 | [84] |
| Extended-release pharmaceutical formulations | US20100160363 | Cardinal JR et al. | 2010 | [85] |
| pH-dependent controlled release pharmaceutical composition for non-opioids with resistance against the influence of ethanol | EP2187875 | Petereit H et al. | 2012 | [86] |
| Oral pharmaceutical tablet for controled release of mesalazine and process for obtaining it | WO/2012/089677,<br>TW201306843 | Loeches BD et al. | 2012<br>2013 | [87]<br>[88] |

## 2.1. Biodegradable controlled release systems

The present invention related to gel-forming macromers including at least four polymeric blocks, at least two of which are hydrophobic and at least one of which is hydrophilic, and including a cross-linkable group are provided. The macromers can be covalently cross-linked to form a gel on a tissue surface in vivo. The gels formed from the macromers have a combination of properties including thermo sensitivity and lipophilicity, and are useful in a variety of medical applications including drug delivery and tissue coating [9, 10, 20].

Biodegradable controlled release microspheres for the prolonged administration of a local anesthetic agent, and a method for the manufacture thereof are disclosed. The microspheres are formed of a biodegradable polymer degrading significantly within a month, with at least 50% of the polymer degrading into non-toxic residues which are removed by the body within a two week period. Useful polymers include polyanhydrides, polylactic acid-glycolic acid copolymers and polyorthoesters containing a catalyst; polylactic acid-glycolic acid copolymers are preferred. Local anesthetics are incorporated into the polymer using a method that yields a uniform dispersion, preferably solvent casting. Prolonged release is obtained by incorporation of a glucocorticoid into the polymeric matrix or by co-administration of the glucocorticoid with the microspheres. The type of anesthetic and the quantity are selected based on the known pharmaceutical properties of these compounds [11-13].

To get a controlled release formulation comprising only a biodegradable polymer material having no control on an environment and having a controlled release rate in an agrochemical formulation prepared by formulating a volatile organic compound having an attracting, repelling or killing action on organisms with a base composed of the biodegradable polymer material. The controlled release formulation can make the release rate of the volatile organic compound constant for a long period of time. Since the biodegradable substance is used, the formulation is decomposed after the passage of use period and recovery is not required [14].

The invention provides implantable medical devices that are fabricated, at least in part, from biodegradable polymeric material. The implantable medical devices are used to provide bioactive agent to a treatment site, and are particularly useful for treatment of limited access regions of the body [15, 16].

The present invention provides stable, self-assembling, biocompatible and biodegradable hydrogel formulations, into which one or more compounds may be incorporated allowing for delayed release or controlled release of the incorporated compounds as the hydrogel is degraded in the body [17].

A biodegradable, multi-layered controlled release gastro retentive baclofen or R-baclofen dosage form which is optionally divided into a first dosage of baclofen or R-baclofen for immediate release and a second dosage of baclofen or R-baclofen for controlled release in the stomach and GI tract of a patient, folded into a capsule which disintegrates upon contact with gastric juice and the dosage form unfolds rapidly upon contact with gastric juice. The biodegradable, multi-layered gastro retentive dosage forms of the invention provide fast onset of baclofen or R-baclofen activity with prolonged absorption and minimal undesirable side effects [18].

In particular, the method provides the contacting of an organic phase containing a bioactive agent and a polymer with an aqueous phase containing an organic ion to create the controlled release compositions containing bioactive agents. The invention also includes the controlled release compositions including a polymer, an organic ion, and a bioactive agent. The present invention also includes methods of using such controlled release compositions. The usefulness of the invention is that the methods result in the production of controlled release compositions containing bioactive agent capable of administration in a concentrated low-dose form, having low burst and reduced production of degraded bioactive agent [19].

### 2.2. Biomucoadhesive controlled release systems

Bioadhesive and controlled release drug delivery systems were prepared from a series of starches grafted with acrylic monomers by two initiation methods: chemical and radiation. These materials can be characterized by measuring their swelling in water and at various pH values and the molecular weight of the branched acrylic polymer grafted onto the starch can also be determined. These materials had better bioadhesive

and controlled drug release properties. The effect of mono- and divalent cations present in the graft copolymers indicated a particularly high potential as bioadhesive materials for oral drug delivery systems [21, 22].

A composite formulation has been developed for selective, high efficacy delivery to specific regions of the mouth and GI tract. The formulation is typically in the form of a tablet or capsule, which may include microparticles or beads. The formulation uses bioadhesive 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 bioadhesive 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. The bioadhesive 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 bioadhesive 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 GI 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 [23].

An oral delivery system comprises a first tooth whitening agent; a second tooth whitening agent or a taste masking agent; and an encapsulating material, which at least partially forms a physical barrier around the first whitening agents and the second tooth whitening agents or taste masking agent [24].

### 2.3. Floating controlled release systems

The oral formulation with controlled release designed to release at least one Betaine after oral administration, characterized in that said formulation comprises or is combined with at least one means ensuring floatability of at least one betaine in the GI tract [25, 26].

A pharmaceutical formulation and its process for the preparation of controlled release gastric floating matrix solid oral dosage form of Imatinib or its pharmaceutically acceptable salts and its polymorphs such as β, & agr 2, Form I and Form 2 thereof for once daily administration in the form of coated tablet or minitablets and / or pellets filled in hard gelatin capsules [27].

The invention discloses a colchicines gastric floating sustained-release tablet, which comprises active components of colchicines and pharmaceutical adjuvant according to the weight ratio of 1:24-1, 999, wherein the pharmaceutical adjuvant comprises a hydrophilic gel framework material, a effervescing agent, a floating assistant material, a filler, a pH value regulator and a lubricant. The colchicines gastric floating SR tablet can swell quickly in gastric juice or a similar gastric juice medium and can float on the gastric juice for at least 4 hours. The colchicines gastric floating sustained-release tablet can reach the effective blood-drug concentration quickly after being taken and then release drugs slowly, and can maintain the balanced blood-drug concentration so as to reduce the dose times, relieve the toxic side effect and improve the bioavailability [28].

The invention relates to a medicament for treating diabetes, in particular to a metformin HCl intra-gastric floating SR tablet preparation with high bioavailability. By adopting a framework-type material, an aerogenic agent, a lubricant, an adhesive and other prescriptions and using a unique preparation process, the invention can overcome solve the problem that sustained-controlled-release tablets in the prior art are low in bioavailability [29].

The invention relates to an intra-gastric floating SR tablet containing floating Konjac glucomannan and preparation method thereof [30].

The invention relates to the field of medicinal preparations, in particular to a method for preparing xanthan gum Omeprazole intra-gastric retention floating SR tablets. According to the method, xanthan gum is used as a skeleton, additives such as a foaming agent are added to improve floating force, and $CO_2$ released when the additives contact gastric acid is wrapped in a gel layer, so that the density of a preparation is easy to reduce or low-density hydrophobic substances are added to reduce the density of the preparation and prevent the hydration of the

skeleton. Water-soluble medicines are prepared into hydrophilic gel skeleton tablets to solve the problem of controlling release speed, the skeleton releases the medicines by a dissolution mechanism, and the medicine release characteristic of an optimizing formula accords with a Higuichi equation, so that the bioavailability of the medicines is improved, and the action time is prolonged [31].

The invention relates to a Ranitidine bismuth citrate intra-gastric floating SR tablet which is composed of a tablet core containing ranitidine bismuth citrate and a coating film wrapped over the tablet core. The tablet core is prepared from raw materials at least containing, by weight, 110 to 120 parts of ranitidine bismuth citrate, 30 to 60 parts of a skeletal material, 5 to 20 parts of a foaming agent and 45 to 130 parts of a bleaching assistant. The coating film accounts for 1 to 5% of the weight of the tablet. The tablet provided by the invention can effectively adjust the rate of constant speed release of the drug ranitidine bismuth citrate and enables a steady and lasting effective plasma concentration to be obtained, so side effects of the drug, frequency of administration and influence of the drug on an in-vivo environment are reduced, and compliance of a patient is improved [32].

The invention relates to the field of medicinal preparations, and particularly relates to a preparation method of a xanthan gum vildagliptin intra-gastric retentive floating SR tablet. Common adverse reactions of vildagliptin comprise headache, hypertension deterioration and the like. Substrates degraded by DPPIV is extensive, so the DPPIV inhibitor has potential effect on blood pressure, immune system, and the like; and the drug has a short half life, so new technology is necessary to the increase of the period with an effective drug concentration, the increase of bioavailability, and the reduction of side effect. The invention adopts xanthan gum as a skeleton, and some additives are added to facilitate the decrease of the preparation density, and the prevention of skeleton hydration. The invention mainly solves the problems of release speed control, drug release from the skeleton by a corrosion mechanism, and optimization of prescription drug release characteristics to meet a Higuichi equation, and thus increases the bioavailability and prolongs the action time [33].

An intra-gastric floating type cuttlebone SR tablet for treating gastric ulcer is prepared from the following raw materials: cuttlebone, nano-montmorillonite, HPMC, octadecanol, MCC and magnesium stearate. Compared with the prior art, the SR tablet overcomes the defect that the residence time of a common oral preparation drug at the nidus part is short. The intra-gastric floating type SR preparation is prepared, so that the reaction rate of calcium carbonate in the cuttlebone and gastric acid can be slowed down as far as possible, and the hyperacidity relief and pain relief time is prolonged. The prepared intra-gastric floating tablet can stay in the stomach for 6-8 hours, so that the release of the tablet is delayed and the absorption is increased. The medicine taking frequency is reduced, and the bioavailability is improved. In addition, the cuttlebone is selected from edible animals of a natural marine, so that the advantages that no toxic or side effects are caused, the safety is high and the like are achieved [34].

### 2.4. Osmotically controlled release systems

The present invention is related to a pH insensitive drug delivery device, specifically an osmotic pump, for the Controlled Release (CR) of a beneficial age not in an environment of use, which comprises (a) a core prepared from an admixture comprising: (i) a therapeutically effective amount of at least one beneficial agent, or salts thereof, that has a solubility profile that is dependent on the pH level of the environment of use; and (ii) at least one pH modulating agent; and (b) a controlled porosity, microporous coating which surrounds the core. In a second embodiment, the invention is also related to a pH insensitive, osmotic drug delivery device for the controlled release of a beneficial agent in an environment of use, which comprises (a) a core containing a therapeutically effective amount of at least one beneficial agent, or salts thereof, that has a solubility profile that is dependent on the pH level of the environment of use; and (b) a controlled porosity, microporous coating which surrounds the core and has at least one aperture [35-38].

The present invention provides a novel floating osmotic device that is capable of delivering a first active agent in an outer coat immediately followed by continuous controlled delivery of second active agent from the osmotic core while the dosage form floats in the fluid of the environment. The floating osmotic device has of a compressed core containing active agent, a semi-permeable membrane surrounding the core that is permeable to surrounding fluid and impermeable to the active agent, and an outer coating of a gas generating ingredient, a gelling agent, and a second active agent. Particular embodiments of the invention provide floating osmotic devices in which all two active agents are similar or dissimilar [39].

The present invention provides an oral osmotic controlled drug delivery system comprising (a) a core comprising a homogeneous mixture of glipizide, a hydrophilic polymer and other pharmaceutically acceptable excipients, (b) a semi permeable wall surrounding the core, said wall being impermeable to the contents of the core, but permeable to fluids present in the environment of use, and (c) a passageway through the wall for release of contents of the core to the environment of use [40].

The invention belongs to the field of medical technologies, in particular to a prescription and a process of a potassium chloride controlled release tablet. The process comprises the following steps of: by adopting EC, PVP, Hypromellose and the like as release blockers, adding an inert excipient, a lubricant and a coloring agent which are pharmaceutical acceptable according to a certain proportion to prepare a core tablet by using a suitable process; then, compounding cellulose acetate with a suitable coating additive to prepare a semipermeable membrane encapsulating the core tablet, and generating a drug release passage on the membrane to form a controlled release system of an elementary osmotic pump type for providing the zero-level release of potassium chloride [41].

## 2.5. Multilayer controlled release tablets

The invention relates to multilayer tablets which are constructed of two, three or more layers, one layer containing probiotic microorganisms, while the other layers contain foodstuff ingredients valuable in nutritional physiology, such as vitamins, minerals, etc. The tablets are distinguished by a high stability or activities over a long period with respect to the microorganisms used and are thus very well suited for keeping in storage [42].

A multilayer tablet 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 [43, 44].

Multilayer tablets of Omeprazole and/or a salt thereof essentially bioequivalent in terms of plasma Omeprazole $C_{max}$ and AUC to Omeprazole capsules and/or Omeprazole Magnesium tablets consisting of multiple unit pellets are provided. Also provided are methods for production of these multilayer tablets and methods for their use in treating dyspepsia, peptic ulcer disease, gastro-esophageal reflux disease and Zollinger-Ellison syndrome [45].

A multilayer oral dosage form that provides controlled release of an active compound includes a non-erodible core containing a pharmaceutically active compound and/or a nutritionally active compound, and at least one release-modulating layer laminated to each side of the core layer. The dosage form can be prepared using simple, inexpensive tablet compression techniques [46].

## 2.6. Diffusion matrix system

The present invention provides a pharmaceutical preparation in tablet form, where the active ingredient is an anti-epileptic medication, preferably a SR formulation, and most preferably a carbamazepine SR formulation. The product consists of carbamazepine particles coated with a single hydrophobic layer and is in a disintegrating tablet form [47, 48].

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrix and finally inglobated or dispersed in hydrophilic matrix. The use of a plurality of systems for the control of the dissolution of the active ingredient

modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the GI tract [49].

CR oral pharmaceutical compositions containing as active agent 5-amino-salicylic acid, comprising: (a) an inner lipophilic matrix consisting of substances with melting point below 90 °C in which the active ingredient is at least partly inglobated; (b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; (c) optionally other excipients [50].

To inexpensively obtain the subject formulation having effectively controlled elution of agrochemical component to the outside of the formulation in a short time by coating a core material with a specific wax emulsion, an agrochemical component and water-repellent powder. This formulation is obtained by coating (d) a core material (preferably various mineral granular substances like quartz sand particle) with (a) an agrochemical component, (b) a wax emulsion having 60 °C melting point and (c) water-repellent powder. Further preferably, after the coating, the coated core material is dried and water contained in an emulsion is removed. Following the drying, the formulation can be granulated by an ordinary granulation means. In the case of 10 ppm, especially 50 ppm of water solubility of the component (a), an elution inhibitory effect can be extremely developed. The amounts of the components added in the formulation are preferably 0.1-80% of the component (a), 1-70 wt % of the component (b) and 0.5-60% of the component (c) [51].

There is disclosed an oral delivery system, which comprises: a sachet at least partially formed from at least one microporous or permeable membrane, and defining a cavity; a physiologically active substance dissolved or dispersed in a liquid or gel, within the cavity, the microporous or permeable membrane being in contact with the liquid or gel and being permeable to the physiologically active substance in the liquid or gel; and an encapsulating layer surrounding the sachet; characterized in that either: (a) the membrane is hydrophilic and the contents of the sachet are hydrophobic; or (b) the membrane is hydrophobic and the contents of the sachet are hydrophilic; whereby, in use, the encapsulating layer is first dissolved in the GI tract and thereafter passage of the physiologically active substance into the GIT through the membrane is rate-controlled. A method of manufacturing the oral delivery system is also disclosed [52].

There is disclosed a zero-order SR delivery of carbamazepine. A matrix tablet formulations of carbamazepine comprising hydrophilic polymer gel which inhibits transformation of carbamazepine into carbamazepine dihydrate by causing morphologic changes of carbamazepine crystals and results in amorphous form of carbamazepine present in the polymer matrix [53].

To provide a dosage form that retains stable elution of medicine under the controlled conditions same as the original conditions, causing no change, even when it is exposed to a variety of temperature and humidity conditions for a long period of time, the pharmaceutical formulation thereof and methods for producing the same. A stabilized solid CR formulation having a coating derived from an aqueous dispersion of a hydrophobic polymer is obtained by over coating a substrate including an active agent selected from the group consisting of a systemically active therapeutic agent, a locally active therapeutic agent, a disinfecting and sanitizing agent, a cleansing agent, a fragrance agent and a fertilizing agent, with an aqueous dispersion of the plasticized hydrophobic polymer and then curing the coated substrate at a temperature above the glass transition temperature of the plasticized hydrophobic polymer, until a curing endpoint is reached at which the coated substrate provided a stabilized elution of the active agent which is unchanged after exposure to accelerated storage conditions [54, 55].

A SR pharmaceutical composition in a form of an orally deliverable tablet comprises 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 kN $cm^{-2}$ at a solid fraction representative of the tablet [56, 60].

The invention provides a dosage form, comprising a melt-processed mixture of (a) a pharmaceutically effective amount of Imatinib or a salt thereof, (b) at least one polymeric binder, and (c) at least one pharmaceutically acceptable non-ionic surfactant. The invention provides Imatinib dosage forms with

high drug loading which can be prepared in a simple and efficient manner, imatinib dosage forms from which the active principle is released in an essentially pH-independent fashion, and extended release imatinib dosage forms [57].

Disclosed herein are CR formulations which exhibit substantially zero-order release kinetics. The formulations include a core comprising a core active agent and a wax excipient substantially coated with an extended-release coating. The formulation optionally includes an Immediate-Release (IR) portion comprising an IR drug in the form of, for example, a coating disposed on at least a portion of the core. Further disclosed are fexofenadine/pseudoephedrine combination formulations, which exhibit substantially no food effect [58, 71].

A SR pharmaceutical composition in a form of an oral tablet containing Reboxetine, or a pharmaceutically acceptable salt thereof, dispersed in a matrix containing a hydrophilic polymer and a starch, wherein the starch has a tensile strength of at least 0.15 kN $cm^{-2}$ at a solid fraction of 0.75 to 0.85 [59].

To provide a solid CR oral formulation suppressing the release rate of an active agent and extending duration of pain relief of a patient after administering the formulation while maintaining the effect of the formulation and reducing times of administration. The formulation includes a core containing inactive pharmaceutical beads applied with an opioid analgesic or a salt thereof and a coating applied on the core. The coating contains an effective amount of a hydrophobic polymer to perform the CR of the opioid analgesic in 24 hours; the hydrophobic polymer is selected from a group consisting of plasticized acrylic polymers, plasticized EC and mixtures thereof. The dosage formulation provides a dissolution profile substantially unaffected in comparison of an initial solubility with solubility after leaving the dosage formulation for 28 days under the condition of 37 $^0$C/80% Relative Humidity (RH) [61].

Disclosed herein do CR formulations of a core comprise a core active agent (e.g., Alfuzosin) and a wax excipient substantially coated with an extended-release coating [62].

To provide a formulation of Octreotide or pharmaceutically acceptable salts thereof, which provide CR of a therapeutically effective amount of Octreotide, which is a drug for treatment of Acromegaly for a period of at least two months. This implant formulation is hydrogel containing octreotide, where the hydrogel has a copolymer obtained by copolymerization of a mixture having at least two hydrophilic ethylenic unsaturated monomers, optionally has hydroxypropylcellulose, and contains 20-150 mg of octreotide in a free form or a salt form. The implant releases octreotide in the body of a patient in an amount of 0.1-9 ng/ml in terms of in-vivo average Css for a period of at least two months [63].

To provides a new solid agrichemical formulation having CR agrichemical active ingredient. The solid agrichemical formulation comprises (a) a granule containing an agrichemical active ingredient and a hydrophobic substance solid at 25°C, (b) an acidic substance and (c) a solid carrier. The acidic substance is especially preferably citric acid, ascorbic acid, benzoic acid or phosphoric acid. Wax, a fatty acid, a fatty acid ester or a resin is preferable as the solid hydrophobic substance solid at 25°C [64].

The present invention provides matrix-forming, SR formulations comprising four primary components: (i) an effective amount of at least one drug substance; (ii) at least one pharmaceutically acceptable, water-swellable, pH independent polymer; (iii) at least one pharmaceutically-acceptable, anionic, pH dependent polymer; and (iv) a pharmaceutically-acceptable polymer selected from the group consisting of (a) at least one pharmaceutically-acceptable cationic polymer; and (b) at least one pharmaceutically acceptable hydrocolloid. The present formulations can be used with compounds having a wide range of solubility as well as compounds characterized as having hydrophobic or hydrophilic characteristics [65].

To provide a biodegradable implant prescribed for control sustainable drug release. Combinations of hydrophilic and hydrophobic entities in a biodegradable SR implant are shown to modulate each other's rate of release. Formulations of a therapeutically active agent and modulator provide substantially constant rate of release for an extended period of time [66].

The present invention provides stable, self-assembling, biocompatible and biodegradable hydrogel formulations, into

which one or more compounds may be incorporated allowing for SR or CR of the incorporated compounds as the hydrogel is degraded in the body [67].

To provide a CR pharmaceutical administration agent form containing, as an effective component, phosphodiesterase 5 inhibitors Vardenafil. The CR pharmaceutical administration agent form is a formulation releasing a permeable pharmaceutical substance, containing a matrix or the like for delivering an effective component via a membrane, a pH modification substance, and diffusion or corrosion of controlling the release of the effective component [68].

The present application relate to pharmaceutical formulations comprising Imatinib or its salts, isomers, racemates, enantiomers, hydrates, solvates, metabolites, and polymorphs, and mixtures thereof. Further aspects relate to processes for preparing pharmaceutical formulations comprising imatinib or its salts, together with at least one pharmaceutically acceptable excipient [69].

### 2.7. Mineral matrix based on porosity

The present invention concerns a particulate 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 [70].

Porous calcium phosphate implant compositions that approximate the chemical composition of natural bone mineral are provided. In addition to calcium phosphate, the compositions include an effervescent agent to promote the formation of interconnected pores and a cohesiveness agent to maintain the shape and hardness of the hardened composition. When introduced at an implant site, the calcium phosphate compositions are remodeled into bone. Methods for using the calcium phosphate compositions, e.g., to repair or replace bone, are also provided [72].

### 2.8. Dissolution sustained - Water soluble matrix system

To obtain a medicine release-control types percutaneous absorptive formulation freely controlled releasing rate of a medicine according to an object of curing, having exceedingly excellent storage stability and high safety without inducing a rush by pasting. A microcapsule comprising a water-soluble wall material including a medicine and a water-insoluble, rubber and rubber solvent-insoluble water-absorptive resin powder (e.g.; starch-polyacrylate graft co-polymer) are mixed and dispersed in a rubber-based tacky adhesive. The rubber-based tacky adhesive is mainly composed of a rubber-adhesive component (e.g.; isoprene-based rubber), a tackiness-imparting agent (e.g.; a petroleum resin) and a plasticizer (e.g.; liquid paraffin). An oily substance not dissolving the wall material is used as the medicine and the wall material is selected from a water-soluble polymer such as gelatin. By microcapsulating the medicine and an absorption accelerator, storage stability of the formulation is high and body fluid is absorbed into ointment by pasting on the skin, then the medicine and the absorption accelerator are eluted by slowly destructing the microcapsule, thereby a medicine release can be controlled by mixing several kinds of microcapsules having different membrane thickness [73].

SR caffeine formulation comprising micro particles have a biodegradable water soluble matrix that are uniformly distributed and to a method of making it [74].

The present invention, CR potassium chloride tablets are prepared from a pharmaceutical composition comprised of potassium chloride particles coated with a membrane of plasticized water swellable or soluble polymer. The coated Potassium chloride particles are blended with pharmaceutical excipients and compressed into tablets [75].

A method of making a SR formulation of water soluble peptides containing a polypeptide, preferably Somatostatin or an analog or derivative thereof, more preferably octreotide, in a polymeric matrix, preferably poly(lactide-co-glycolide) glucose is

provided. The SR formulation can exhibit drug serum levels having therapeutic activity over a predetermined period [76].

The invention provides CR formulations having a coated core with the core comprising a drug-containing and a water-swellable composition, each occupying essentially separate regions within the core. The drug-containing composition comprises a PDE4D inhibitor, and a drug-entraining agent. The coating around the core is water-permeable, water-insoluble, and has at least one delivery port there through. The invention further provides methods of reducing the nausea and emetic effects of PDE4D inhibitors, and CR formulations having improved PDE4D inhibitor in vivo and in vitro profiles [77].

In the present invention, a new pharmaceutical formulation with CR of the freely water soluble low-dose active substance used for at the most once daily administration is disclosed. The active substance is maintained at a suitable therapeutic concentration in the blood throughout at least a 24 hour period independent of the physiological pH value to which the pharmaceutical formulation is exposed [78].

The invention proves a novel compressed tablet of a pharmaceutical compound and a method of making a tablet of a pharmaceutical compound which are based on uncoated pellets containing a pharmaceutical compound that are dispersed in a matrix which comprises said pellets and a swellable polymer which is compressed into a tablet that is coated with an enteric polymer [79].

The present application discloses a SR composition in pellet form, wherein the core of the pellet comprises: (a) a therapeutically effective amount of a medicament; (b) 0.5 to 50% by weight of a water-soluble polymer; and (c) 1 to 25% by weight of a water-insoluble polymer applied as an aqueous latex dispersion and subsequently the water is removed, wherein the sum of the percentages of the medicament, the water-insoluble polymer and the water-soluble polymer is equal to or less than 100% [80].

A CR formulation with zero-order release comprises: (a) a core containing at least one drug; (b) a CR coating membrane coated outside of the core. The CR coating membrane comprises at least one polymer insoluble in water and GI digestive fluid and a cyclodextrin derivative, wherein the cyclodextrin derivative is a water-soluble cyclodextrin derivative with an average substitution value of no less than 5 of the hydroxyl group on each glucose unit, and disperses in the controlled release coating membrane in single molecular form and/or in micellar form. The drug release from the CR formulation is relatively less affected in vivo and in vitro and is relatively faster with a relatively smaller time lag. The bioavailability of the drug is higher, the stability of the drug release is increased, and the mechanical strength of the controlled release coating membrane of the formulation is also increased [81].

### 2.9. pH sensitive matrix systems

The present invention provides a CR formulation comprising an therapeutically effective amount of pharmacologically active substance having high water solubility, at least one non-polymeric release retardant, and at least one pH independent non-swelling release retarding polymer. The said dosage form provides CR of the active agent with reduced initial burst release [82, 83].

The present invention relates to orally delivered, CR preparation of insulin and other bioactive materials encapsulated in polymeric microspheres. The pH sensitive polymeric microspheres comprising Eudragit are provided. Method for delivering drugs to the lower GI tract, while avoiding exposure to the stomach acids is provided. Methods for treating diabetes using CR insulin delivery particles are provided [84].

The present invention provides matrix-forming, SR formulations comprising four primary components: (i) an effective amount of at least one drug substance; (ii) at least one pharmaceutically acceptable, water-swellable, pH independent polymer; (iii) at least one pharmaceutically-acceptable, anionic, pH dependent polymer; and (iv) a pharmaceutically-acceptable polymer selected from the group consisting of (a) at least one pharmaceutically-acceptable cationic polymer; and (b) at least one pharmaceutically acceptable hydrocolloid. The present formulations can be used with compounds having a wide range of solubility's as well as compounds characterized as having hydrophobic or hydrophilic characteristics [85].

The pH-dependent controlled release pharmaceutical composition for non-opioids with resistance against the influence of ethanol [86].

The invention provides an oral pharmaceutical tablet for CR 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 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 to say oral CR pharmaceutical tablet of mesalazine for treating ulcerative colitis [87, 88].

## 3. Marketed Pharmaceutical Controlled Release Products

**Table 2:** Marketed controlled release products

| Composition | Product Name | Manufacturer |
|---|---|---|
| **1. Tablet** | | |
| Diclofenac sodium | Dic – SR | Dee Pharma Limited |
| Diclofenac sodium | Mobinase – SR | Crosland |
| Diclofenac sodium | Monovac – SR | Boehringer – Mannheim |
| Diclofenac sodium | Relaxyl - SR | Franco – Indian |
| Diltiazem HCl | Diltime SR | Alidac |
| Diclofenac sodium | Dicloram SR | Unique |
| Diclofenac sodium | Doflex SR | Nicholas Piramal |
| Lithium carbonate | Lithosun – SR | Sunpharma |
| Nifedipine | Nyogard LA | Searle (I) Ltd |
| Nifedipine | Calcigard Retard | Torrent |
| Nifedipine | Depin Retard | Cadila Health Care |
| Salbutamol, Theophylline | TheoAsthalin SR | Cipla |
| Diclofenac sodium | Voveran – SR | Ciba – Geigy |
| Theophylline | Theo PA | Welcome |
| Diclofenac sodium | Nac – SR | Systopic |
| Diclofenac sodium | Agile – SR | Swift |
| Carbamazepine | Zen Retard | Intas |
| Theophylline Anhydrous | Theo Stan – CR | Stancare |
| Diltiazem | Dilzem SR | Torrent |
| Terbutaline Sulphate, Theophylline Anhydrous | Theobric – SR | Remidex |
| Diazepam | Calmrelease – TR | Natco |
| Verapamil hydrochloride | | Calpatin SR |

| | | |
|---|---|---|
| Verapamil hydrochloride | Calapatin 240 SR | Boehringer – Mannheim |
| **2. Capsules** | | |
| Chlorpheniramine maleate, Phenylepinephrine Hydrochloride | Coldvir – SR | Dee Pharma Ltd |
| Diclofenac sodium | Diclotal CR | Blue Cross |
| Diazepam | Elcoin | Ranbaxy |
| Diclofenac sodium | Nalco TR | Natco |
| Dried Ferrous Sulphate, Folic acid | Feron SR | Dee Pharma Ltd |
| Dried Ferrous Sulphate, Folic acid | Fefol Spansules | Eskayef |
| Dried Ferrous Sulphate, Folic acid, Ascorbic acid | Ultiron – TR | Stancare |
| Dried Ferrous Sulphate, Folic acid, Vit. B12, Vit. C, Vit. B2 | Convinon TR | Ranbaxy |
| Indomethacin | Indoflam TR | Recon |
| Isosorbide Dinnitrate | Cardicap TR | Natco |
| Ketoprofen | Profenid CR | Rhone– Poulenc |
| Ferrous Fummarate, Zinc Sulphate Monohydrate | Ziberrin – TR | Recon |
| Flurbiprofen | Arflur SR | FDC |
| Nifedipine | Nicardia | J. B. Chemicals & Pharmaceuticals |
| Nifedipine | Indocap SR | J. B. Chemicals & Pharmaceuticals |
| Nifedipine | Cardules Retard | Nicohlas Piramal |
| Nitroglycerin | Angispan TR | Lyka |
| Vitamin C, B2, B1, Nicotinamide, Pantothenic acid, Dried Ferrous Sulphate | Pesovit Spansules | Eskayef |
| **3. Transdermal** | | |
| Estrogen | Estraderm TTS | Ciba – Geigy |
| Nitroglycerine | Nitorderm TTS | Ciba – Geigy |
| Nicotine | Nicotine Patch | Ciba – Geigy |

## 4. Current & Future Developments

The design of oral controlled release systems has been a challenge to formulated research scientists due to their need of ability to control and localize the arrangement at targeted areas of the GI tract. Controlled release formulations using alternative routes have been formulated other than the oral route still remains the most advantageous. On behalf of clear reason, water soluble drugs are more not easy to convey orally in sustained or controlled release way than lipophilic drugs. Attempts have been ready to regulate the release process by incorporating hydrophobic fillers surrounded by the system or by coating the drug with poorly soluble, swollen or non-swollen polymers or additional substances. Others used the so called “floating hydrodynamically balanced systems (HBS)” which float in the gastric fluid at the stomach thus increase the gastric residence time for the device in the GI tract. A new approach has been the

use of mucoadhesive system to augment the gastric residence time of the mechanism inside the GI tract.

This review focuses on the advancement completed in the design of controlled or sustained release delivery for numerous water soluble drugs. For example, highly or freely water soluble diltiazem, captopril and morphine salts etc., comprise selected as model drugs due to the important function they play into their relevant meadow of treatment and their extensive use into treating chronic patients. Scrupulous prominence is given toward delivery systems designed to achieve their once a day dose treatment. Significant advances have been attained in developing and commercializing oral controlled release products. Lots of platforms are accessible for deliver small molecule drugs among good aqueous solubility into extended or delayed release forms. On the other hand, there are important challenges in mounting controlled release formulations designed for drugs with poor aqueous solubility, which need together solubilization and engineering of release profile.

To convey drugs at zero-order release rate, rather independent of the GI tract environment, lots of efforts and achievements have been made besides osmotic pump drug delivery systems. Furthermore, lots of the new therapeutics under development is large molecules like peptides, proteins, oligonucleotides, and vaccines. Their physical, chemical, and biopharmaceutical attributes, distinct from small molecule drugs, insist novel controlled-release technology to reduce barriers for oral delivery like instability in the GI tract and poor absorption.

Those unmet technology needs create great opportunity designed for research, development, and innovation. Breakthroughs into controlled oral delivery designed for water-insoluble drugs and biopharmaceuticals are probable toward contain momentous impact on the pharmaceutical and biotechnology industries. On the other hand, the constant development of present delivery technology is too important when it comes to decreasing cost and increasing efficiency. Those advancements comprise narrative excipients, processes, and equipment as novel tools formulation scientists can use to develop oral controlled-release formulations.

These patents have been reviewed to demonstrate the variety of the controlled or sustained release drug delivery. These systems grip a leading market share in the drug delivery products as demonstrate by means of the number of products in the market and patents granted in the most recent few years. As a result of modulating assorted formulation aspects, it is probable toward use these systems to carry drugs of diversify nature at a pre-programmed rate.

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