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Advancement in Sustained Released Dosage form for Oral Drug Delivery

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Abstract: The most frequent route of medication delivery is orally. It is the favored method due to the benefits such as non-invasiveness, patient compliance, and ease of medication delivery. Several variables influence oral medication absorption, including drug solubility, mucosal permeability, and gastrointestinal tract stability. Efforts to overcome these hurdles have centered on understanding the physicochemical, biochemical, metabolic, and biological limitations that restrict total medication bioavailability. To improve oral medication absorption, many pharmaceutical technologies and drug delivery systems such as nanocarriers, micelles, cyclodextrins, and lipid-based carriers have been investigated. However, the conventional dose form has a few restrictions that might be overcome by changing the present dosage form. Sustained and regulated drug delivery systems aid in the maintenance of steady plasma drug concentrations and slow the rate of drug release, therefore extending the duration of effect. There are several formulation options for sustained release tablets, with matrix tablet being a key tool. As a result, issues such as poor patient compliance, repeated doses, and see-saw swings may be readily mitigated. Matrix tablets can be made utilizing a range of hydrophilic or hydrophobic polymers by direct compression or wet granulation. The rate of drug release from the matrix is essentially determined by the pace and degree of water penetration, polymer swelling, dissolution, and drug diffusion. As a result, prolonged release matrix tablets may improve patient compliance and be beneficial in the treatment of chronic disorders. The current review focuses on oral sustained release tablets, with a particular emphasis on matrix tablets.

Keywords: Sustained release, Oral drug delivery, Conventional tablet, Controlled release, Dosage form

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Introduction

To achieve a systemic approach to the successful development of an oral pharmic, all pharmaceutical products formulated for systemic delivery via the oral route of administration, regardless of the

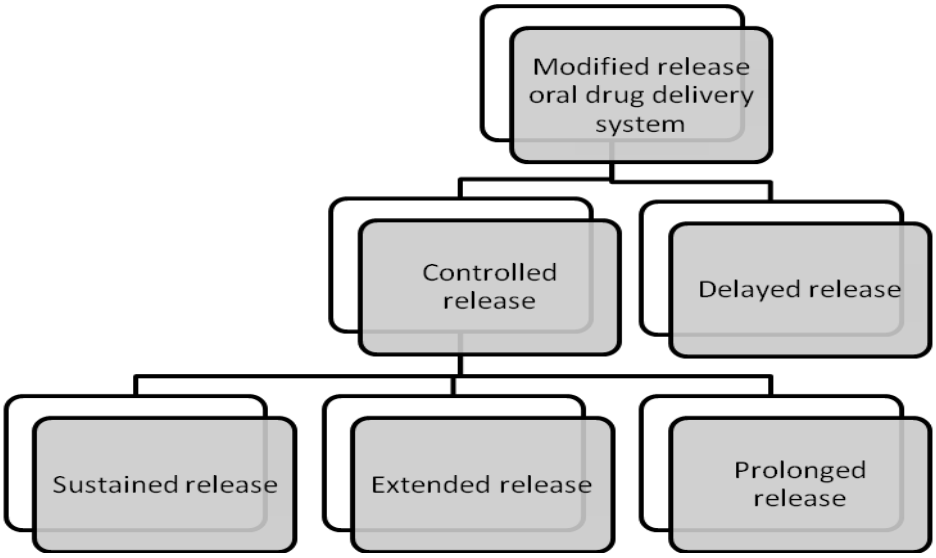

Fig. 1: Modified release oral drug delivery system.

mode of delivery (immediate, sustained, or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmaco-dynamics, and formulation design (Chien 1992; John and Morten, 2002; Mandal *et al.*, 2010; Dixit *et al.*, 2013; Lokhande *et al.*, 2019). For some time, the Pharmaceutical industry has recognised the benefits of providing a single dose of a medicine that is delivered over a long period of time rather than many doses. The history of medication administration dosage forms may be dated back to 1938.

This review concerns coated pallets for extended drug release and was most likely a precursor to the invention of the coated particle technique to sustained drug administration, which was developed in the early 1950s (Chugh *et al.*, 2012). This unique drug delivery system provides a technique of increasing the therapeutic efficacy of included pharmaceuticals by delivering sustained, regulated distribution and/or targeting the medication to the desired place (Stuti *et al.*, 2011). The purpose of any drug delivery system is to deliver a therapeutic amount of medicine to the appropriate place in the body in order to attain and then maintain the intended drug concentration (Jantzen and Robinson, 1996). Any medication delivery technique that accomplishes gradual release is considered a sustained release system. A controlled-release system is one that is successful in maintaining consistent medication levels in the blood or target tissue (Brahmankar and Jaiswal, 1995; Jantzen and Robinson, 1996) (Fig. 1).

SUSTAINED RELEASE DOSAGE FORM:

Sustained release dosage form is described as a well-characterized and repeatable dosage form that is meant to manage the drug release profile at a set pace in order to obtain the appropriate drug concentration in blood plasma or at the target site. This system will give therapeutic control that is either temporal (time-related), spatial (site-related), or both (Agarwal and Kaushik, 2012; Agrwal *et al.*, 2017).

Advantages of Sustained Release Drug Delivery System (SDDS):

- See-saw fluctuations have been reduced.
- The total dosage is reduced.
- Better patient compliance.
- Improved medication safety (Hadi *et al.*, 2012; Zalte and Saudagar, 2013; Pundir *et al.*, 2013).

Disadvantages of SDDS:

- Dose retrieval is difficult.
- Chances of dose dumping

- Need for additional patient education
- Reduced potential for accurate dose adjustment
- High cost for formulation

Classification of Oral Sustained Release Systems:

Controlled release systems for oral use are generally solids that employ dissolution, diffusion, or a mix of both methods to regulate medication release rate. These systems are categorised as follows based on the method of drug release:

(1) *Continuous release System*:

With standard dosage form transportation, continuous release systems release the medicine for a prolonged amount of time over the whole length of the gastrointestinal tract. The following systems fall within this category:

(A) Diffusion-controlled release mechanisms

(B) Dissolution controlled release systems

(C)Controlled release systems based on evaporation and diffusion

(D) Drug-ion exchange resin complexes

(E) Formulation that is pH-independent

(F) Systems with osmotic pressure control (Vyas and Khar, 2002).

(A) *Diffusion-controlled release systems*:

The diffusion of dissolved drug via a polymeric barrier is a rate limiting step in these systems. Because the diffusional route length grows with time as the insoluble matrix is gradually depleted of drug, the drug release rate is never zero-order. The controlled drug delivery systems are based on the diffusion of a drug molecule via a polymeric membrane (Shilhusen *et al.*, 2014).

(B) *Dissolution-controlled release systems*:

The medication found in such a system may be the one Having a high water solubility and rate of dissolution. Slowing the dissolution rate of a medication in the GI medium, embedding the drug in an insoluble polymer, and covering drug particles or granules with polymeric materials of varied thickness can all result in dissolution-controlled release (Modi *et al.*, 2011; Patel *et al.*, 2013). The diffusion over the aqueous boundary layer is the rate limiting stage in drug dissolution.

(C) *Controlled release systems based on evaporation and diffusion*:

The drug core is wrapped in a partially soluble membrane in such systems. Pores are formed as a result of the dissolving of sections of the membrane, allowing aqueous medium into the core and hence drug dissolution, as well as the diffusion of dissolved drug out of the system (Gandhi and Hari Kumar, 2014).

(D) *Drug-ion exchange resin complexes*:

Ion-exchange resin complexes, which may be made from both acidic and basic medicines, have been extensively researched and commercialized. Salts of cationic and anionic exchange resins are insoluble complexes in which drug release is caused by the interchange of bound drug ions with ions found in bodily fluids.

(E) *Formulation that is pH-independent*:

For pharmaceuticals with pH-dependent solubility, the pH of the dissolving media influences the pace and amount of drug release from most controlled release devices. This reliance on pH for medication release may result in significant inter- and intra-subject variability in drug absorption.

(F) *Systems with osmotic pressure control*:

The main material in an osmotic system flows down a solute concentration gradient through a semi-permeable membrane. Water may readily pass through the pores of such a membrane, but not the solute. The difference in solute concentration on one side draws water over the barrier.

(2) *Delayed transit and continual release system*:

These systems are designed to prolong release of drug with increased residence time in GIT. Such

dosage forms are designed to remain in the stomach. Therefore the drug presented in such systems should be stable at gastric pH (Jain, 2002; Lokhande *et al*., 2019).

(3) *Delayed release System*:

These systems are fabricated to release the drug only at specific site in the GIT. The drugs those are:

- Destroyed in stomach or by intestinal enzymes
- Known to cause gastric irritation
- Absorbed from specific site in intestine are formulated in such systems (Sahilhusen *et al.*, 2014; Lokhande *et al*., 2019).

Various mechanisms of Medicament Release:

(1) *Diffusion is rate limiting*:

Diffusion is a strong force that happens when medication molecules travel from a high concentration in the tablet to a lower concentration in the gastro intestinal fluids (Rajesh *et al.*, 2012). This movement is determined by the surface area exposed to stomach fluid, the diffusion pathway, the drug concentration gradient, and the system's diffusion coefficient.

In practice, we can use one of two methods:

(a) The medication is formed in an insoluble matrix; stomach fluid penetrates the dosage form, dissolves the medicament, and liberates the drug

by diffusion.

(b) The drug particles are coated with a polymer of a certain thickness, allowing the drug to slowly diffuse through the polymer and maintain a steady drug level in the blood ((Rajesh *et al.*, 2012)).

(2) *Osmotic pressure is rate limiting*:

Osmosis is a phenomena in which liquid flows from low concentration to high concentration via a semipermeable membrane that permits only liquid transfer. The entire medicine is covered with a semipermeable membrane, with a laser beam creating a hole on one end of the tablet. The gastric fluid permeates the membrane, solubilizes the medication, and raises the internal pressure, forcing the drug solution out of the aperture and releasing it into the stomach environment (Modi *et al.*, 2011).

BIOPHARMACEUTICAL PROPERTIES OF SDDS:

Molecular weight:

Absorption will be quicker and more complete when the molecular weight is reduced. The molecular size threshold for pharmaceuticals absorbed by pore transport mechanism is 150 Daltons for spherical compounds and 400 Daltons for linear compounds. For passive diffusion, the maximum molecule size is 600 Daltons.

Aqueous solubility of the drugs:

Drugs with high water solubility are better options for sustained release dosage forms than those with low aqueous solubility.

Apparent partition coefficient of drug:

The bigger the drug's apparent partition coefficient, the greater the rate and extent of absorption.

Drug pka and ionization at physiological pH:

Acidic medications have a pka range of 3.0-7.5, while basic pharmaceuticals have a pka range of 7.0-11.0. The pka of the chemical and the pH of the medium influence aqueous solubility of weak acids and bases. According to pH theory, acidic medications absorb better in acidic environments while basic pharmaceuticals absorb better in basic environments. As a result, the release of ionizable medicines must be programmed in line with pH fluctuations throughout the GIT. As a result, medications that reside mostly in ionised state are poor candidates for sustained release dosage form (Wise, 2000).

Drug Stability:

Drugs that are unstable in the GI tract are poor choices for oral sustained release systems.

BIOPHARMACEUTICAL ASPECTS OF ROUTE OF ADMINISTRATION:

The most common methods are oral and parental

(i.m.), followed by transdermal. Buccal/sublingual, nasal, rectal, ocular, and pulmonary routes are minor in sustained drug administration (Vyas and Khar, 2002). A thorough understanding of the ADME properties of the medicine is required for the creation of a sustained release product. An ideal range of a drug's specified pharmacokinetic characteristic is required, beyond which controlled/sustained administration is impossible (Tahara *et al.*, 1995; Shargel *et al.*, 1999; Mehta, 2002; Tonnesen and Karlsen, 2002; Kamboj *et al.*, 2009; Joshi *et al.*, 2012). Active components and sustained-release materials are typically combined into sustained release agents with specific physical forms in the actual application of SRTs. Tablets, capsules, film agents, microspheres, pellets, and other forms of sustained release agents are common.

Tablets:

Tablets are round or irregular flaky solid agents made by combining active substances with appropriate ingredients (Ford *et al.*, 1985; Reddy *et al.*, 2003). Because of their simplicity of preparation, they have been widely used in continuous release and controlled release agents. This category includes medications such as isosorbide mononitrate sustained-release tablets and nifedipine release controlled tablets (Antipov *et al.*, 2001). Coating tablets have occupied a certain position as a sustained-release agent due to the continual development of macromolecular technologies. Coating tablets is primarily responsible for keeping tablets from being impacted by air, oxygen, and moisture, allowing them to maintain long-term stability and achieve the sustained release aim of active components in the target medium (Shi *et al.*, 2016).

Capsules:

Capsules are solid agents made by compressing active ingredients into hollow hard capsules or sealing them in elastic soft capsules (Shi *et al.*, 2016). They have been widely used because of their capacity to mask the unpleasant taste and odour of active components, increase their stability, and solidify liquid-state active components (Liu *et al.*, 2017). For example, in the manufacture of Ibuprofen sustained release agent, Zhao *et al.* (1995) suspended particles by pumping compressed air into a spray-drying coating equipment and coated particles with ethylcellulose acetone solution. Yao *et al.* (1999) produced Etoposide microcapsule particles using chitosan and sodium alginate as carriers and packed them into regular capsule shells using a sophisticated coacervation process. Xia *et al.* (1999) combined sodium carboxymethylcellulose, stearic acid, and sodium bicarbonate with diclofenac sodium, packed the mixture into empty capsule shells, cooked them, and then made Diclofenac sodium gastric floating-type sustained-release tablets. Yang *et al.* (1998) employed the film-coating approach to create acemetacin controlled-release pellets, which they then used to create acemetacin-containing capsules. Martinac *et al.* (2002) developed sustained release microspheres using chitosan, poly [(,-(N-2-bis-hydroxyethyl-dl-asparagine)] and poly [(,-(N-3-hydroxypropyl-dl-asparagine)]. Zhang *et al.* (2018) used self-assembly to create eugenol-gelatin-chitosan nanocapsules using gelatin and chitosan as carriers.

Microcapsules:

Microcapsules are created by covering solid or liquid active components (capsule core materials) with natural or synthetic macromolecular compound materials (capsule materials) used to create the capsule film wall shell (Saifullah *et al.*, 2019). When active components are dissolved and/or disseminated in macromolecular materials, skeleton-type microsphere entities known as microspheres arise. Because the particle size of a microcapsule and a microsphere is between 1 and 250 m, they belong to the micron order and are collectively referred to as microparticles. Manjanna *et al.* (2010) produced Aceclofenac sustained release microspheres using alginate as the hydrophobic carrier and calcium chloride as the cross-linking agent. Alginate was chosen as a coating material by because of its

sustained release performance and high biocompatibility mucous film microcapsules and employed sodium carboxymethylcellulose as mucous film adhesive. The micro-encapsulation efficiency was high, and the adhesion was good. To achieve sustained-release medication delivery, the two were combined in the right quantity. Fan *et al.* (2006) developed econazole nitrate microspheres using gelatin and Arabic gum as capsule ingredients. Feng *et al.* (2004) used the degradable polymer polylactic acid as the carrier to create leuprorelin sustained release microspheres. Yang *et al.* (2004) used a simple coacervation process to manufacture propafenone in sustained-release microcapsules utilising gelatin as the capsule material. Vallbacka *et al.*, 2001 created microcapsules that could release dopamine using hydroxyethyl methacrylate-methyl methacrylate as the capsule material. An *et al.* (2004) employed a layer-by-layer construction process to encapsulate ibuprofen for drug-controlled release using human serum albumin and L-dimyristoylphosphatidic acid as capsule shell materials.

Film Agent:

Thin-film agents are created by dissolving or evenly distributing medicines into film-forming ingredients (Manna and Patil, 2008; Chong *et al.*, 2017). Yan and Zou (1998) prepared compounds with protective films and drug films before preparing tinidazole one-way sustained release films with polyvinyl alcohol, glycerin, and water as protective film components and Arabic gum powder, tinidazole, sodium bicarbonate, tetracaine, bezoar detoxicating tablet, azone, glycerin, and water as drug film components. Tinidazole sustained release films were created by Zhou (1999) using tinidazole, sodium carboxy-methylcellulose, and polyvinyl alcohol as film ingredients.

Preparation methods of sustained release agents:

Sustained release agents are classified as either skeleton or reservoir (Aulton *et al.*, 2013). Drugs are disseminated uniformly in diverse carrier materials in the form of molecules, microcrystals, and microparticles, resulting in skeleton-type sustained release agents; drugs are wrapped in macromolecular polymer films, resulting in reservoir-type sustained release agents. Table 1 summarises the formulation methods and principles of typical sustained release agents.

ADVANCEMENT IN SUSTAINED RELEASE ORAL DOSAGE FORM:

The advancement in sustained release oral dosage form is performed by the various researchers like Amoxycillin trihydrate sustained-release (SR) tablets, several hydrophilic polymers was developed by Hilton and Deasy (1992). The best method had a 1:2 hydroxypropylcellulose (HPC) to medication ratio that compacted smoothly and was unaffected by changes in typical compaction pressure. Intrinsic dissolving tests at pH 2 revealed that decreasing drug loading reduced drug release, which was linear with time, indicating an eroding matrix with a hydrated layer. An examination of compacts across a larger pH range revealed the slowest rate of drug release at pH 6, matching to the drug's minimal solubility. Further formulation to improve gastric retention time (GRT) by including a gas-generating device resulted in either bilayer tablets that failed early or big single-layer tablets that stayed buoyant for 6 h and had good *in vitro* SR. However, when the later tablets were compared to normal capsules in fasting people at 500 mg equivalent dosage of amoxycillin, their relative bioavailability was lowered to 80.5%, and other pharmacokinetic metrics showed a lack of increased effectiveness (Hilton and Deasy, 1992).

The new approach was applied to flurbiprofen, adinazolam mesylate, and alprazolam SR dosage forms, which have a wide range of drug solubility and formulation composition by Skoug *et al.* (1993). The superimposable drug and polymer release patterns of SR flurbiprofen tablets imply that the mechanism is predominantly an erosion controlled process. The mechanism of action of SR adinazolam mesylate tablets is virtually entirely regulated by diffusion. When the drug is entirely

Table 1: Formulation methods and principles of typical sustained release agents (Wang *et al.*, 2019)

Morphology of Sustained Release Agent	**Preparation Method**	**Preparation Principles and Features**
(Micro)capsule	Complex coacervation	Two macromolecular molecules with opposite charges are taken as composite capsule materials which cross-link with each other under certain conditions and experience coacervation with capsule core to form capsules.
	Simple coacervation	Coagulant is added in macromolecular capsule material solution to reduce macromolecular solubility for coacervation into capsules.
	Solvent/non-solvent method	According to the solubility principle, target substance is firstly dissolved in a solvent, followed by necessary operations, and then non-solvent chemicals are added so that target substance is precipitated out in the form of crystallization or wrapping on other material surfaces.
	Drying in liquid technique	The volatile solvent in the disperse phase is removed from the emulsion to prepare microcapsules (microspheres).
	Spray drying method	After thinner is atomized in a drying room, moisture will be rapidly vaporized when thinner contacts hot air so as to obtain the dry product. This method can directly dry solution and emulsion into powdery or particulate products, thus saving evaporation, crushing and other procedures.
	Spray congealing	After being dissolved with a proper solvent, the drug is blended with the molten carrier, and the product can be obtained after cooling and congealing.
	Self-assembly method	The principle of molecular self-assembly is to use molecular recognition between a molecule pair or fragment pair to form a class of molecular polymers with a specific structure, stability, and specific properties through non-covalent interaction.
	Fluidized bed coating	Capsule core is suspended in the coating room through vertical strong airflow. Capsule solution is sprayed onto the surface of capsule core through a nozzle so that hot airflow resulting in the suspension of capsule core volatilizes the solvent until it becomes dry, and then thin capsule film is formed on the surface to obtain microspheres.
	Multiorifice-centrifugal process	Drug obtain centrifugal force through a high-speed revolution cylinder. The drug solution passes through the capsule material at a high speed to form a liquid film which is then solidified through different methods to obtain microspheres.
	Supercritical fluids	The drug solution is dispersed in supercritical fluid through the nozzle of a supercritical fluid device, the organic solvent is dissolved in a supercritical fluid and then extracted, and the remaining drug is formed into microspheres.
	Spinning disk atomization	The material enters a disk spinning at a high speed through the material supply tube. Under high-speed shear action, it leaves the edge of the disk and solidified

		after being cooled at the bottom, thus forming microspheres.
	Interface polycondensation	Capsule film is generated due to monomer polycondensation reaction on the interface of the disperse phase (aqueous phase) and continuous phase (organic phase), thus forming microspheres.
	Chemical radiation	γ-ray energy generated by ^{60}Co is used for cross-linking and congealing of polymer (gelatin or polyvinyl alcohol) so as to form microspheres.
Adsorption of sustained release solid	Adsorption method	Active substances are adsorbed through many pores or high specific surface area to reach the sustained release effect.
Tablets/particles	Drying or wetting method for particle/tablet preparation	Skeleton material, drug, and other ingredients are blended to directly prepare particles/tablets, and in some cases, the adhesive or wetting agent is used to help the particle/tablet preparation.
Solid dispersion	Solid dispersion method	The drug is incorporated into a solid carrier under a highly dispersed state through certain methods (melting method, solvent method, and mechanical dispersion method).
Nanoparticles	Emulsion polymerization	The monomer is firstly dispersed in aqueous capsule emulsion droplets containing an emulsifier, it is polymerized into nanoparticles using methods such as high-energy radiation and then turned into the solid state after phase separation, and then solid nanoparticles are prepared.
	Natural polymer condensation method	Natural macromolecular (like protein and polysaccharides) solution containing active components is added into the oil phase and then water/oil emulsion is formed through mechanical agitation or ultrasonic dispersion. Macromolecules are condensed through chemical cross-linking, thermotropy or dehydration by salting-out under proper conditions, thus forming nanoparticles.

released, only approximately 35% of the polymer has dissolved, and the larger variability of the polymer profile is not reflected in the drug release profile. In the case of SR alprazolam tablets, both diffusion and erosion contribute to the total drug release mechanism. At the conclusion of the dissolving test, around 60-70% of the polymer had dissolved, and the variability of the polymer release data is reflected to some extent in the drug release data, notably between the 4 and 8-h time intervals and for the higher tablet strengths. With increased dosage, erosion appears to contribute to the total release mechanism to a greater extent. Jain *et al*. (2008) made Furosemide sustained release tablets with pectin, guar gum, and xanthan gum. The tablets were tested for physical properties such as hardness, weight fluctuation, brittleness, and drug content. For 15 h, medication was released *in vitro* in PBS pH 7.2. The physical characteristics of the manufactured tablet were all within permissible limits. The swelling index was higher in the guar gum tablet than in the pectin and xanthan gum tablets. The matrix tablet (G4) consisting of guar gum produced a better regulated drug release (80.74%) than pectin and xanthan gum. It is cleared by the dissolution profile of furosemide from matrix tablets made with various natural polymers that were delayed for about 15 h. Radhika *et al.* (2009) created a novel monolithic matrix tablet that entirely delivers glipizide in a zero order way over a long period of time two techniques were investigated, both of which used the medicine in a formulation including polymers such as hydroxylpropyl

methylcellulose K 100 (HPMCK) and Eudragit L 100. The granules were formed using the wet granulation process and were designated as F-1 and F-2. F-3 and F-4 bring up polymers with other constituents by employing the aforementioned. Angle of repose, loose bulk density and tapped density, compressibility index, total porosity, and drug content were all measured in granules from various formulations.

Oral sustained drug delivery system for Metoprolol succinate employing natural hydrophilic gums such as karaya gum and xanthan gum is used as a release modifier by Deshmukh *et al.* (2009). Nine batches were made utilising karaya gum (KG) and xanthan gum (XG) at concentrations of 15%, 20%, and 25% alone and in a 2:8 combination. Wet granulation was used to create matrix tablets, which were then tested for weight variation, content homogeneity, friability, hardness, thickness, swelling index, *in vitro* dissolution, and stereo photography. Among the formulations investigated, formulation F8 with a mix of KG and XG (2:8) at a concentration of 20% demonstrated sustained drug release for 12 h with a total percent release of 99.24%. The kinetic treatment revealed that the improved formulation has a zero order kinetic with a release exponent (n) of 0.7656 and high stability according to ICH criteria. IR investigations revealed no chemical interaction between the medication and the gums. The diffusion mechanism enabled Metotprolol succinate to be released continuously from the matrix formulation F8.

Salbutamol and theophylline traditional dose formulations that are delivered four times per day, resulting in saw tooth kinetics and poor treatment. The combination of these two medications in a single dose form will improve patient compliance while also extending bronchodilation. Several polymers were investigated, including hydroxy propyl methylcellulose K4M (HPMC- K4M), hydroxy propyl methylcellulose K100M (HPMC-K100M), xanthan gum, ethyl cellulose, and hydroxy propyl methylcellulose phthalate (HPMC-P). HPMC-P and HPMC-K4M were found to be the most effective in controlling the release. All bi-layered tablets created were subjected to *in vitro* dissolving investigations using the USP dissolution equipment type 2 (paddle). It was discovered that the tablet FB15-FW3 released 50% of the salbutamol within the first hour, with the remainder released over the next 8 h. However, theophylline was discovered to be released in accordance with USP requirements. The IR spectra of the FB15-FW3 formulation demonstrated no disruption in the main peaks of the pure medicines salbutamol and theophylline. This establishes the purity of pure medicines and their incompatibility with excipients. Furthermore, the FB15-FW3 formulation demonstrated the needed release pattern, complied with all of the tested criteria, and was equivalent to the marketed formulation (Nagaraju and Kaza, 2009).

Sustained release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymer was formulated and evaluated by Wadher *et al.* (2011). Sustained release formulations that sustain plasma levels for 8-12 h may be enough for daily metformin dosage. Metformin requires sustained release products to prolong its duration of action and increase patient compliance. The ultimate goal of this work was to create an oral sustained release metformin hydrochloride tablet employing hydrophilic Eudragit RSPO alone or in conjunction with hydrophobic natural polymers Gum copal and gum damar as rate regulating factors. The pills were created using the wet granulation process. The data was analyzed using the zero order, first order, Higuchi, Korsmeyer, and Hixson-Crowell equations, and the *in vitro* dissolution investigation was conducted out using USP 22 apparatus I, paddle technique. According to the drug release research, Eudragit RSPO alone was unable to maintain drug release. When Eudragit was combined with gum Copal and gum Damar, the medication was released for more than 12 h. The drug release mechanism spans from diffusion regulated or Fickian transport to anomalous type or non-Fickian transport, according to kinetic modelling of *in vitro* dissolution patterns. Fitting

the *in vitro* drug release data to the Korsmeyer equation revealed that drug release might occur via diffusion and erosion.

Owusu *et al.* (2019) used *Capparis erythrocarpos* to treat arthritis. *Capparis erythrocarpos* powder is recommended and supplied to patients in Ghana for the treatment of arthritis. *Capparis erythrocarpos* controlled release tablets were effectively manufactured using the wet granulation process in this investigation. In varied ratios of (1;1), (1;2), and (1;3), hydroxypropyl methyl cellulose and Xanthan gum were utilised as drug release modulating polymers. The formed tablets passed the weight uniformity, friability, thickness uniformity, and diameter uniformity tests.

Oral sustained release gastroretentive dose forms several advantages for pharmaceuticals absorbed through the upper gastrointestinal tract and increase the bioavailability of treatments with a narrow absorption window provided by Gangurde *et al.* (2011). The current study sought to develop a sustained release bioadhesive gastroretentive ofloxacin dosage form. To investigate the drug release profile and bioadhesive strength, a 32 complete factorial design was used. The drug release mechanism was discovered to be abnormal in the majority of the formulations, including the improved formulation. The radiographic imaging demonstrated that the tablet retains its structural integrity and form in the stomach for up to 24 h. The improved formulation underwent short-term accelerated stability testing, and the findings demonstrated that the drug content, *in vitro* dissolution, and all other parameters were within acceptable ranges.

Lornoxicam, a very effective nonsteroidal anti-inflammatory medication with a short half-life, making the creation of sustained release (SR) versions exceedingly desirable (Ulla *et al.,* 2011). However, because to its low acidity, its release via SR delivery methods is restricted to the lower gastrointestinal tract, resulting in a delayed commencement of analgesic activity. As a result, the goal of the study was to create Lornoxicam SR matrix tablets that give total drug release that begins in the stomach to quickly relieve painful sensations and continues in the intestine to sustain analgesic efficacy. Lornoxicam had the greatest absorption at 373 nm in 0.1N HCl and 379 nm at pH 6.8. Shanmungam *et al.* (2011) created sustained release matrix tablets containing Losartan potassium, an antihypertensive medication. Wet granulation was used to create the sustained release tablets, which were then compounded with various drug and polymer ratios, resulting in formulations ranging from F1 to F9. theyemployed hydrophilic polymers such as Hydroxypropyl methylcellulose (HPMC), hydrophobic polymers such as Ethyl Cellulose (EC), and natural polymers such as Xanthan Gum (XG). The drug's compatibility with various excipients was investigated. The final composition generated tough tablets with excellent hardness, weight homogeneity, and friability. Rohit *et al.* (2015) formulated and evaluated sustained release tablets using cashew gum and cross-linked cashew gum as controlled release polymer. To optimise the formulation, a full factorial design of 23 was used. As independent variables, cashew gum (CG), cross-linked cashew gum (CCG), and microcrystalline cellulose (MCC) were used. The dependent variables chosen were the percentage of drug released in the first hour (Y1), the percentage of drug released in the 12^{th} hour (Y2), and the diffusion exponent n. (Y3). Direct compression was used to create tablets, and powder qualities were tested, revealing rather excellent flow properties. The weight variation, hardness, friability, medication content, and dissolving profile of prepared tablets were all assessed.

Levosulpiride gastroprokinetic drug is used in the treatment of a variety of gastric problems; nevertheless, its short half-life and increasing dosing frequency which result in noncompliance and potential side effects (Samie *et al.*, 2018). The primary goal of the study was to create a sustained-release formulation of Levosulpiride that included bioresorbable cellulose derivatives. Levosulpiride sustained-release formulations

were created employing direct compression and various cellulose derivatives such as CMC sodium, HPC, and HPMC in various polymer-to-drug weight ratios as release-modifying polymers. Prakhar *et al.* (2018) aimed to develop and test ibuprofen sustained release tablets. Hydroxy-propyl and ethyl cellulose are matrix polymers that can be employed in the formulation of a prolonged release dosage form of a medication that is just minimally water soluble. Ibuprofen was thought to be the best medicine for a prolonged release formulation. Wet granulation was used to create an Ibuprofen sustained release matrix with different matrix polymer ratios. The Active Pharmaceutical Ingredient has undergone pre-formulation tests. Drug excipient compatibility experiments were conducted, and tablets were manufactured in seven distinct formulations with varied excipient ratios. Dissolution tests are used to analyse these tablets for a variety of criteria, including drug release. As a consequence of the research, Ibuprofen Sustained Release was created Release tablets comparable to the innovator product for Ibuprofen which is stable.

Oral controlled drug delivery systems are the most common type of long-term drug delivery systems for the obvious advantages of the oral route of drug administration (Malviya *et al.*, 2019). These methods deliver the medication at constant or variable rates. Oral controlled release systems exhibit a characteristic pattern of drug release in which the drug concentration is maintained in the therapeutic window for an extended period of time (sustained release), ensuring long-term therapeutic activity. They are administered as a single dose. This study entails the synthesis and analysis of Zolmitriptan Hydrochloride beads employing Sodium alginate as a natural polymer, as well as Hydroxyl Propyl Methyl Cellulose K15 and Chitosan Hydrochloride. Ionotropic gelation is the procedure used to produce the drug beads.

Conclusion

Based on the foregoing explanation, it is easy to deduce that sustained-release formulations aid in enhancing dosage efficiency while also improving patient compatibility. Sustained release, on the other hand, refers to the steady release of a substance over time. Sustain-release formulations can be regulated or uncontrolled. We may conclude from the preceding discussion that the formation of SRDDS is dependent on a number of factors, including biopharmaceutics, pharmaco-kinetic and pharmacodynamic drug properties. As an alternative for oral predictable drug delivery systems, sustained release drug delivery systems have had little difficulties in entering the market. With the detailed literature review we concluded that future sustained-release technologies should progress in the direction of accurate, quantitative, biotechnology-integrated, and intelligent sustained-release, with efforts focused on resolving biodegradability and recycling issues with carrier materials. Concerning the water treatment sector, which is receiving a lot of attention right now, several technological difficulties in the implementation process, such as secondary contamination and interface passivation, must be solved. As a result, high-performance, cost-effective, non-toxic, harmless, second-pollution-free, photo-triggered, and smart sustained-release agents will have a wide range of applications in the field of environmental restoration.

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References

Agarwal G, Agarwal S, Karar PK and Goyal S. (2017) Oral sustained release tablets: an overview with a special emphasis on matrix tablet. Am J Adv Drug Deliv. 5: 64-76.

Agarwal G and Kaushik A. (2012) Pharmaceutical technology-II. CBS Publishers, New Delhi.

An Z, Lu G, Möhwald H and Li J. (2004) Self-assembly of human serum albumin (HSA) and l-α-dimyristoylphosphatidic acid (DMPA) microcapsules for controlled drug release. Chem Eur J. 10: 5848-5852.

Antipov AA, Sukhorukov GB, Donath E and Möhwald H. (2001) Sustained release properties of polyelectrolyte multilayer capsules. J Physical Chem

B. 105: 2281-2284.

Aulton ME and Taylor K. (2013) Aulton's pharmaceutics: the design and manufacture of medicines. Elsevier Health Sciences.

Brahmankar DM and Jaiswal SB. (1995) Biopharmaceutics and pharmacokinetics-a treatise. Vallabh Prakashan, New Delhi.

Chien YW. (1992) Novel drug delivery systems. M. Dekker, New York.

Chong Y, Ge C, Fang G, Wu R, Zhang H, Chai Z, Chen C and Yin JJ. (2017) Light-enhanced antibacterial activity of graphene oxide, mainly via accelerated electron transfer. Environ Sci Technol. 51: 10154-10161.

Chugh I, Seth N, Rana AC and Gupta S. (2012) Oral sustained release drug delivery system: an overview. Int Res J Pharma. 3: 57-62.

Deshmukh VN, Singh SP and Sakarkar DM. (2009) Formulation and evaluation of sustained release metoprolol succinate tablet using hydrophilic gums as release modifiers. Int J Pharm Tech Res. 1: 159-163.

Dixit N, Maurya SD and Sagar BP. (2013) Sustained release drug delivery system. Indian J Res Pharma Biotechnol. 1: 305.

Fan RZ, Wan YL and Song WD. (2006) Microcapsule characteristics of econazole nitrate. J Guangdong Coll Pharm. 22: 121-122.

Feng L, Guo JX, Ping QN, Lu J and Zhou J. (2004) Study on sustained-release leuprorelin microspheres. Chinese J New Drugs Clin Remedies 23: 680-683.

Ford JL, Rubinstein MH and Hogan JE. (1985) Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. Int J Pharmaceut. 24: 327-338.

Gandhi A and Hari Kumar SL. (2014) Recent trends in sustained release drug delivery system. Int J Interdiscipl Multidiscipl Stud. 1(6): 122-134.

Gangurde HH, Chordiya MA, Tamizharasi S, Senthilkumaran K and Sivakumar T. (2011) Formulation and evaluation of sustained release bioadhesive tablets of ofloxacin using 32 factorial design. Int J Pharmaceut Invest. 1: 148.

Hadi MA, Lokeswara Babu V, Pal N and Srinivasa Rao A. (2012) Formulation and evaluation of sustained release matrix tablets of montelukast sodium. Int J Pharm. 2: 574-582.

Hilton AK and Deasy PB. (1992) In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. Int J Pharmaceut. 86: 79-88.

Jain NK. (2002) Controlled and novel drug delivery. CBS Publisher, New Delhi.

Jain S, Yadav SK and Patil UK. (2008) Preparation and evaluation of sustained release matrix tablet of furosemide using natural polymers. Resh J Pharm Tech. 1: 374-376.

Jantzen GM and Robinson JR. (1996) Sustained-and controlled-release drug delivery systems. Drugs Pharmaceut Sci. 72: 575-610.

John C and Morten C. (2002) The science of dosage form design, aulton: modified release peroral dosage forms. 2nd edn., Churchill Livingstone.

Joshi J, Bhakuni L and Kumar S. (2012) Formulation and evaluation of solid matrix tablets of repaglinide. Der Pharm Sin. 3: 598- 603.

Kamboj S, Gupta GD and Oberoy J. (2009) Matrix tablets: An important tool for oral controlled-release dosage forms. Pharmainfo Net 7(6): 1-9.

Liu X, Appelhans D, Wei Q and Voit B. (2017) Photo-cross - linked dual - responsive hollow capsules mimicking cell membrane for controllable cargo post - encapsulation and release. Adv Sci. 4: 1600308.

Lokhande SS, Phalke NN and Badadare SS. (2019) A review on sustained release technology. World J Pharma Med Res. 5: 60-65.

Malviya VR, Pande SD and Bobade NN. (2019) Preparation and evaluation of sustained release beads of zolmitriptan hydrochloride. Res J Pharma Technol. 12: 5972-5976.

Mandal S, Ratan GN, Mulla JS, Thimmasetty J and Kaneriya A. (2010) Design and in vitro evaluation of gastro retentive sustained release tablets of tizanidine hydrochloride. Int New Drug Deliv. 2: 144-152.

Manjanna KM, Kumar TP and Shivakumar B. (2010) Calcium alginate cross-linked polymeric microbeads for oral sustained drug delivery in arthritis. Drug Discov Therapeut. 4: 109-122.

Manna U and Patil S. (2008) Encapsulation of uncharged water-insoluble organic substance in polymeric membrane capsules via layer-by-layer approach. J Physical Chem B. 112: 13258-13262.

Martinac A, Filipović-Grčić J, Barbarić M, Zorc B, Voinovich D and Jalšenjak I. (2002) Gemfibrozil encapsulation and release from microspheres and macromolecular conjugates. European J Pharmaceut Sci. 17: 207-216.

Mehta RM. (2002) Pharmaceutics. Vallabh Prakashan, New Delhi.

Modi SA, Gaikwad PD, Bankar VH, Pawar SP. (2011)

Sustained release drug delivery system: a review. Int J Pharma. Res Dev. 2:147-60.

Nagaraju R and Kaza R. (2009) Formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline. Int J Pharmaceut Sci Nanotechnol. 2: 638-646.

Owusu FW, Boakye-Gyasi ME, Mante PK, Ekuadzi E, Ofori-Kwakye K and Woode E. (2019) Formulation and evaluation of sustained release matrix tablets of capparis erythrocarpos roots extract to improve patient compliance in management of arthritis. Scientific African 6: e00172.

Patel JS, Thakkar D, Patel KN and Patel KJ. (2013) A review on bilayer tablets. J Drug Discov Therapeut. 1 (3): 40-48.

Prakhar A and Akhtar S. (2018) A comprehensive review on sustained release matrix tablets: a promising dosage form. Universal J Pharmaceut Res. 3: 49-54.

Pundir S, Badola A and Sharma D. (2013) Sustained release matrix technology and recent advance in matrix drug delivery system: a review. Int J Drug Res Tech. 3: 12-20.

Radhika PR, Pal TK and Sivakumar T. (2009) Formulation and evaluation of sustained release matrix tablets of glipizide: Sustained release matrix tablets of glipizide. Iranian J Pharmaceut Sci. 5(4): 205-214.

Rajesh A, Harish R and Sangeeta A. (2012) Sustained released drug technology: A review. Int J Res Pharma Sci. 2(4): 1-13.

Reddy KR, Mutalik S and Reddy S. (2003) Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech. 4(4): 480-488.

Rohit RB, Riyaz Ali MO, Padmaja C and Afrasim MO. (2015) Formulation and evaluation of sustained release dosage form using modified cashew gum. Int J Pharm Pharmaceut Sci. 7(4): 141-150.

Sahilhusen IJ, Mukesh RP and Alpesh DP. (2014) Sustained release drug delivery systems: A patent overview. Aperito J Drug Designing Pharmacol. 1: 1-4.

Saifullah M, Shishir MR, Ferdowsi R, Rahman MR and Van Vuong Q. (2019) Micro and nano encapsulation, retention and controlled release of flavor and aroma compounds: A critical review. Trends Food Sci Technol. 86: 230-251.

Samie M, Bashir S, Abbas J, Khan S, Aman N, Jan H and Muhammad N. (2018) Design, formulation and in vitro evaluation of sustained-release tablet formulations of levosulpiride. Turkish J Pharmaceut Sci. 15: 309.

Shanmugam S, Chakrahari R, Sundaramoorthy K, Ayyappan T and Vetrichelvan T. (2011) Formulation and evaluation of sustained release matrix tablets of Losartan potassium. Intl J Pharm Tech Res. 3: 526-534.

Shargel L, Andrew BC and Wu-Pong S. (1999) Applied biopharmaceutics and pharmacokinetics. Stamford, Appleton and Lange.

Shi D, Ran M, Huang H, Zhang L, Li X, Chen M and Akashi M. (2016) Preparation of glucose responsive polyelectrolyte capsules with shell crosslinking via the layer-by-layer technique and sustained release of insulin. Polymer Chem. 7: 6779-6788.

Skoug JW, Mikelsons MV, Vigneron CN and Stemm NL. (1993) Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. J Controlled Release 27: 227-245.

Stuti G, Ravindra PS and Rohitashva S. (2011) Osmotic pumps: A review. Int J Comprehensive Pharma. 2: 1-8.

Tahara K, Yamamoto K and Nishihata T. (1995) Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. J Controlled Release 35: 59-66.

Tønnesen HH and Karlsen J. (2002) Alginate in drug delivery systems. Drug Develop Indust Pharma. 28: 621-630.

Ulla SN, Roy AK and SM VK. (2011) Formulation and evaluation of sustained release matrix tablets of lornoxicam. Int J Drug Develop Res. 3(1): 31-44..

Vallbacka JJ, Nobrega JN and Sefton MV. (2001) Tissue engineering as a platform for controlled release of therapeutic agents: implantation of microencapsulated dopamine producing cells in the brains of rats. J Controlled Release 72: 93-100.

Vyas SP and Khar RK. (2002) Controlled drug delivery concepts and advances. Vallabh Prakashan.

Wadher KJ, Kakde RB and Umekar MJ. (2011) Formulation and evaluation of a sustained-release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymers. Indian J Pharmaceut Sci. 73: 208.

Wang L and Liu X. (2019) Sustained release technology and its application in environmental remediation: a review. Int J Environ Res Public Hlth. 16: 2153.

Wise DL. (2000) Handbook of pharmaceutical controlled release technology. CRC Press.

Xia YY, Tao ZL, Zheng XX and Lai SF. (1999) Preparation of diclofenac sodium gastric floating sustained release capsule. China Pharm J. 19: 628-629.

Xiao Z, Zhang Y, Zhu G, Niu Y, Xue Z and Zhu J. (2017) Preparation of micro-encapsulated strawberry fragrance and its application in the aromatic wallpaper. Polish J Chem Technol. 19: 89-94.

Yan HY and Zou CC. (1998) Preparation of one-way sustained-release compound tinidazole film and its release characteristics. China Pharm. 9: 249-250.

Yang C and Liu BS. (2004) The trituration of slow-released microcapsule propafenone and test of 1st solubility in vitro. Strait Pharm J. 16: 17-19.

Yang J, He G and Li L. (1998) Study on the release progress and preparation of controlled release capsules of acemetacin. Chinese J Hospital Pharma. 18: 20-21.

Yao FM, Feng CY, Cai CC, Liu LJ, Liu HC and Hou YN. (1999) Preparation of a new-type of etoposide capsules and study of its dissolubility. China Pharm. 10: 106-107.

Zalte HD and Saudagar RB. (2013) Review on sustained release matrix tablet. Int J Pharma Biol Sci. 3: 17-29.

Zhang L, Zhang J, Ma L, Wang Q and Ding W. (2018) Preparation and characterization of eugenol nanocapsules by self-assembly method. Shipin Kexue/Food Sci. 39: 198-204.

Zhao GL and Wang HC. (1995) Drug release kinetics of ibuprofen coated granules and their in vitro-in vivo correlation. Acta Pharmaceut Sinica 30: 291-297.

Zhou YN. (1999) Preparation of tinidazole sustained release membrane for dental teeth. China Hosp. Pharm J. 19: 368-369.