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REVIEW ON PULSATILE DRUG DELIVERY SYSTEM AND THEIR MARKETED PRODUCT

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ABSTRACT

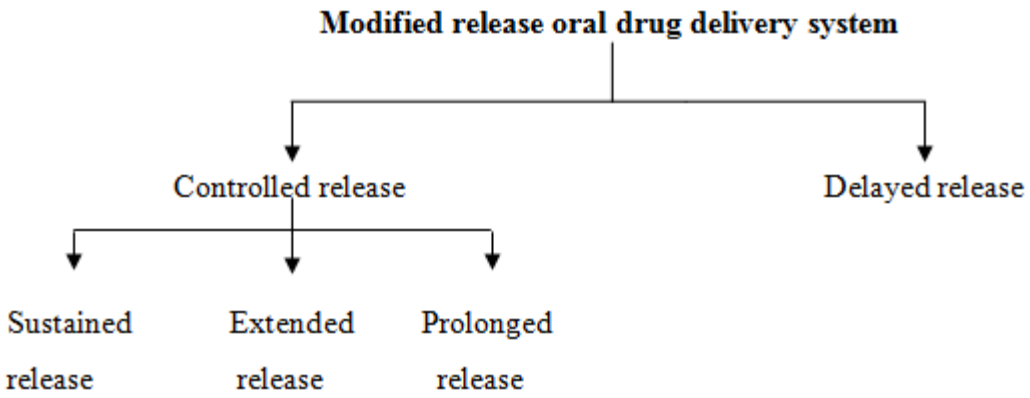
Pulsatile drug delivery system is one of the important system. It deliver the drug at the specific amount as per the pathophysiological need of the disease. Diseases where in Pulsatile drug delivery systems are promising include asthma, peptic ulcer cardiovascular diseases, arthritis attention deficit syndrome in children, and hypercholesterolemia. PDDS is best for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract. PDDS reduces the dosing frequency so now a days it gaining more popularity and the patient compliance. The major challenge in this drug delivery system is to maintained the proper lag time by using suitable technique, and using the different polymers. For coating the suitable polymers on the tablet it is possible to controlled the lag time of the formulation. This review contains the classification, Design and Manufacturing concept, Optimization, evaluation, modeling approaches Material and Marketed product of pulsatile drug delivery system.

KEYWORDS: Pulsatile drug delivery system, Chronomodulated, Design and Manufacturing, Evaluation, polymer, marketed product.

A) INTRODUCTION OF DRUG DELIVERY[1-3]

In the past year the conventional drug delivery system was used for the administration of the drug. But after it was found that the it produces large toxicity in the blood because it get release the drug immediately so the concentration of the drug into the blood plasma goes to the toxic level. To avoid this problem modified drug delivery are discovered which maintain the therapeutic level of the drug in plasma and maintain the constant release of the drug at particular site. The following are the classification of the modified drug delivery system.

The classification of the Drug Delivery System as following



Controlled-release dosage forms

They are class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner for longer period of time.

Sustained release

These are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug.

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

Prolonged release system

They are designed to release the drug slowly and to provide a continuous supply of drug over an extended period. They prevent very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration.

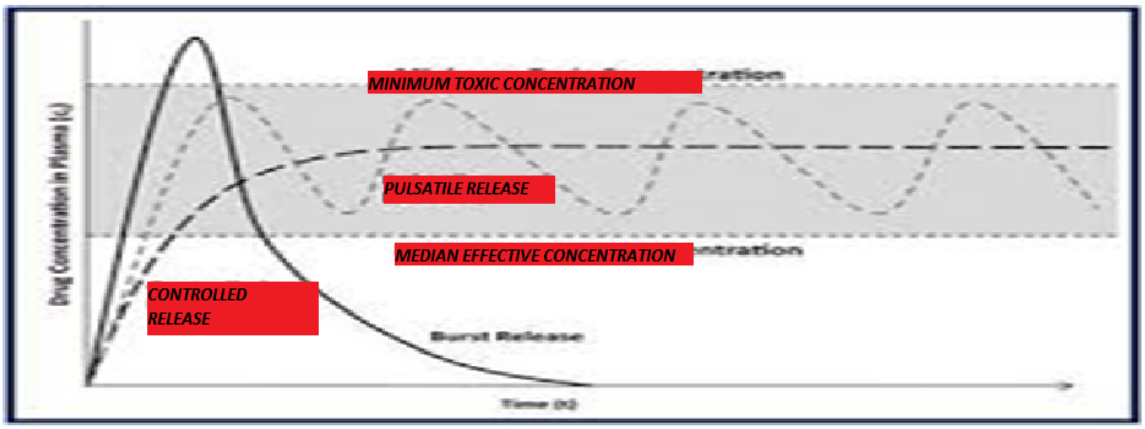
Delayed release

Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form.

Pulsatile drug Delivery System

In conventional therapy drug is released immediately after medication. So, the drug concentration in the plasma is raised. The target of drug discovery is to obtain maximum drug

efficacy and minimum side effect. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs. The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle. Pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time. This method is good for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time, thus provide spatial and temporal delivery and increasing patient compliance, have generated increasing interest during recent years for a number of diseases and therapies.



Rationale of PDDS[4-6]

Advantages

1. Less inter- and intra-subject variability.
2. Improves bioavailability.
3. Reduced adverse effects and improved tolerability.
4. Limited risk of local irritation.
5. No risk of dose dumping.
6. Flexibility in design.
7. Ease of combining pellets with different compositions or release patterns
8. Improves stability.
9. Improves patient comfort and compliance.
10. Achieves a unique release pattern.
11. Extended daytime or night time activity.

12. Reduction in dose size
13. Drug targeting to specific sites like colon.
14. Protection of mucosa from drugs which are irritating.
15. Drug loss is prevented by extensive first pass metabolism

Disadvantages

1. Large number of process variables
2. Batch manufacturing process
3. Low drug loading.
4. Proportionally higher need for excipients.
5. Lack of manufacturing reproducibility and efficacy.
6. Multiple formulation steps.
7. Higher cost of production.
8. Need of advanced technology.
9. Trained / skilled personnel needed for manufacturing

IDEAL CHARACTERISTICS OF CHRDDS[6]

1. It should be non-toxic within approved limits of use.
2. Should have a real-time and specific triggering biomarker for a given disease state.
3. It should be Biocompatible and biodegradable.
4. Easy to manufacture at economic cost.
5. Easy to administer in to patients.

Limitation[8,9]

1. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
2. Low drug loading capacity and incomplete release of drug.
3. In vivo variability in single unit pulsatile drug delivery system.
4. Drug dose manipulation in case of child and elder patients is not possible.
5. Immediate withdrawal of drug is not possible.
6. Used technologies are very complicated

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM (PDDS)[8,10]

(I) Time controlled pulsatile release

(A) Single unit system

1. Osmotic pressure based systems

- Based on expandable orifice
- Based on solubility modifications
- PORT systems

2. Capsular systems
3. Pulsatile system with rupturable coating
4. Pulsatile system with erodible or soluble barrier coatings.

(B) Multi-particulate system

1. Time controlled explosion systems
2. Osmotic based rupturable coating system
3. Rupturable coating systems
4. Pulsatile Delivery by Change in Membrane Permeability
5. Sigmoidal release systems.

(II) Stimuli Induced

(A) Thermo-responsive pulsatile release

1. Temperature controlled systems.

(B) Chemical stimuli induced pulsatile systems

1. Inflammation induced systems
2. Glucose sensitive systems
3. pH based systems
4. Gel based systems

(III) Externally regulated pulsatile release

(A) Electro responsive pulsatile release

(B) Micro electro mechanical systems (MEMS)

(C) Magnetically induced pulsatile release

(D) Ultrasounds.

(E) Mechanical force

(F) Electric field

(G) Light

(IV) Pulsatile release systems for hormone products and vaccine

B) DESIGN AND MANUFACTURING CONCEPT OF THE PDDS[11]

During the designing of the pulsatile drug delivery system to select accurate component required for the delivery system is very important task. In PDDS the majorly following components are added.

1) **Drug core**
2) **Solvent**
3) **Polymer**

1) Drug core

Drug core is mainly prepared by using the inert material such as inert sugar sphere, during the preparation of the drug core some other excipient also added into the formulation such as diluents and the binder agent. by using rotogranulating technique drug containing cores are prepared. Above that sphere or bead about 60-95% drug should be loaded.

Drug selection criteria of PDDS as follows[6,7]

1. Drug should be act locally.
2. It should have absorption window in GIT.
3. It should have an extensive first pass metabolism
4. It should develop biological tolerance.
5. It should develop zero order release
6. It should be non toxic.
7. It should be biocompatible and biodegradable.

2) Solvent

Solvent mainly useful for the dissolve the polymeric agent which have to coat onto the core material. The coating agent selected and dissolve and disperse into the suitable solvent and then coat over the core material. The solvent select depending upon the requirement and properties of the coating material**. E.g.** ethanol (95%), dichloromethane etc.

3) Polymer

For maintained the required delay time over the drug core polymer coating are done. There are water soluble or insoluble polymer selected as per the requirement. When the dosage form goes into the liquid medium, liquid enters into the polymer and release the drug as mechanism such as Diffusion, Erosion, or Osmosis. For that purpose select the accurate

polymer is very important depending upon their hydrophilic or hydrophobic nature.. Carbomer, Guar gum, Carnauba wax etc.

Manufacturing of PDDS

The manufacturing process of the PDDS is vary depending upon the dosage form such as tablet, capsule, etc. so while the manufacturing of the delivery system the major thing is the dosage form selection. in both tablet and capsule formulation following steps include.

1. Drug core/compartment
2. coating over the core compartment

1. Drug core/compartment:

The core is prepared by compressing the blend into the tablet compression machine may be the direct compression method or by preparing the granules. In capsule formulation the drug is spray on the sugar sphere at the desired amount.

2. Coating over the core compartment

After the preparation of the drug core over that gives the coating at the required delay time by using the polymer composition of the different ratio. In the capsule after the coating the core compartment these all packed into the capsule. By spraying different thickness of the coating sphere in to the one capsule helps to produce different time interval of the drug release.

C) DIFFERENCE OF DRUG DELIVERY SYSTEM

Sustained release

It is the type of dosage form in which the portion i.e.(initial dose) of the drug release immediately after the administration of the dosage form. In order to achieve the therapeutic effect promptly and the remaining is then release slowly by achieving a therapeutic level which is which is prolonged but not maintained constant. sustained release implies the release of drug over prolonged period of time. It may or may not be controlled release. It controls the drug entry to the body according to the specification of the required drug delivery profile.

Controlled drug delivery system

It deliver the drug at a predetermined rate for a specific period of time. It is zero order release that is drug release over time irrespective of the concentration. In this system drug rate and duration are not designed to achieve a particular profile.

Pulsatile release

In this system the drug is release after the sufficient lag time. The drug release after the lag time is mainly dependent upon the different body's function. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs.

D) OPTIMIZATION OF THE PDDS

The optimization of the PDDS is mainly based on the disease state and the biological rhythm Of the body such as.

1) Circadian rhythms in diseases, some of these disease show worst conditions in morning and others in night, pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

2) Circadian rhythm which fallows body functions i.e.alter in their release e.g.: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.

3) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting. In such disease condition its very important to release the drug at that particular site when there is change in the bodys rhytm. There are some following diseases which follows Chronological behavior.

BIOLOGICAL RHYTHMS[5]

1. Ultradian Rhythms: Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.

2. Infradian Rhythms: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.

3. Circadian rhythms

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle.

Circadian rhythm and the manifestation of clinical disease.[5,12,13]

Sr. No	Disease	Chronological behavior	Drug used
1	Asthma	Exacerbation more common during the sleep period& attacks at early morning	β2 agonist, Antihistamines
2	Rheumatoid arthritis	Morning and night pain	NSAIDs, Glucocorticoids
3	Myocardial Infraction	In early morning	Cardiovascular drugs e.g. Verapamil, propanolol, diltiazem
4	Stroke	In early morning	Antiplatelet agent
5	Diabetes mellitus	Blood sugar level increase after the meal	Sulfonylurea, Insulin, Biguanide
6	Peptic ulcer	More acid secretion in night and afternoon	H2 blockers
7	Angina Pectoris	More chest pain in morning	Anti anginal drugs
8.	Neurological disorder	the central pathophysiology of epilepsy and behavior of the convulsant event	MAO-B inhibitor

E) EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM[11,14]

Thickness and diameters: It is measured by using vernier calliper in mm.

Hardness: The hardness of tablet was measured by using monsanto hardness tester. The unit of hardness is kg/cm2.

Friability: Friability of tablet was found to be USP friabilator. First of all tablet batch was weighed and placed in friabilator for 100 revolution in 4 minutes. The % friability was calculated by

$F = (Wi-Wf)/ Wi\times100$

Where, Wi = initial weight

Wf = final weight

Weight variation test: The weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average Weight variation limit.

Average weight of tablet (mg)	Maximum difference
80mg or less	10 %
More than 80 mg but less than 250 mg	7.5%
250 mg or more	5%

Lag time and Drug release: The lag time and drug release studies was carried out in gastric and intestinal fluids at body temp. This test is performed in USP dissolution apparatus, in this test the tablet was placed in dissolution media and the sample was withdrawn at specific time interval and after that analyzed in UV spectroscopy.

Rupture test: The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time.

Drug content: In this test accurately weight amount of powder was dissolved in water and filtered. After that the absorbance was measured at fixed wave length by UV spectrophotometer.

Swelling index: The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately Percentage swelling index (SI) was calculated by using the formula

SI = (Wet weight – Dry weight / Dry weight) X 100.

Folding Endurance: This test carried out to check the plasticizer strength and efficiency by using different concentration. A strip of film (2 x 2 cm) is cut evenly and repeatedly folded at the same place until it breaks. The number of times counted until film could be folded at the same place without breaking, this is gave the value of folding endurance. The test is carried out in triplicate.

Different modeling approaches for disease[15]

1. **Modeling cardiovascular diseases-**

$$\frac{dn_{mi}}{dt} = 29.3\text{-}6.74\ \mathrm{Cos}\left(\frac{2\pi \times t}{24}\right) + 5.03\ \mathrm{Sin}\left(\frac{2\pi \times t}{24}\right) + 0.78\ \mathrm{Cos}\left(\frac{2\pi \times t}{24}\right) - 3.55\ \mathrm{Sin}\left(\frac{2\pi \times t}{24}\right) \quad \ldots. \text{ eq.1}$$

Where, $\frac{dn_{mi}}{dt}$ = Number of myocardial infarctions per hour.

t= time of day in hour.

Harmonic regression equations (eq. 1) are used to describe this modeling e.g. in case of frequency of onset of myocardial infarction according to creatine -kinase MB (CK-MB) activity

2. Modeling cancer chemotherapy

Lumped parameter (e.g. Gompertz Model) and cell cycle models are applied to describe tumor growth as well as its behavior respectively. Differential equations of each cell cycle are provided in following equations

XG0 = - (TG0 + dG0)XG0(t) + 2rTMXM(t) …….eq. 2

XG1 = - (TG1 + dG1)XG1(t) + 2(1-r)TMXM(t) …….eq. 3

Xs = - (Ts + ds)Xs(t) + TG1XG1(t) …….eq. 4

XG2 = - (TG2 + dG2)XG2(t) + TsXs(t) …….eq. 5

XM = - (TM + dM)XM(t) + TG2XG2(t) …….eq. 6

Where,

Xi = number of cells in a particular stage.

Ti = transition rate between stages.

di = death rate for cells in a particular stage.

r = enter the resting stage.

(1-r) = return to the RNA/protein synthesis stage

3. Modeling glucose insulin interaction

Low order structured and physiological based model are used to estimate glucose and insulin as given following eq. (7,8,9)

$$\frac{dG(t)}{dt} = (P1 - X(t))G(t) - P1Gb \ldots\ldots. eq.7$$

$$\frac{dX(t)}{dt} = P2X(t) + P3I(t) \ldots\ldots. eq.8$$

$$\frac{dI(t)}{dt} = E(t) - nI(t) \ldots\ldots. eq.9$$

Where,

G(t) = plasma I(t) = Plasma insulin

X(t) = insulin concentration in a remote compartment

E(t) = exogenous insulin

Pi = parameters

Gb = Basal glucose concentration

4. Modeling other diseases

Equations (eq. 10) are developed for biochemical markers require for other diseases.

$f(t) = M + A\cos(\omega t + \emptyset) + ei$ ……..eq. 10

Where,

$f(t)$ = pharmacokinetic/pharmacodynamic (PK/PD)

M = mesor (midline value about which oscillation occur)

A = amplitude (half the differences between the highest and lowest values)

ω = the angular frequency.

Release Kinetics

Release models such as zero-order, first order, Higuchi and Peppa's- Korsemeyer equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics.

1) **Zero order release kinetics:** The plot of % drug release versus time.

$F = K_O t$

Where,

'F' is the drug release at time't',

'Ko' is the zero order release rate constant.

2) **First order release kinetics:** A plot of log cumulative percent of drug remaining to be released vs. time.

$\ln(1-Q) = -K1t$

3) **Higuchi equation:** In higuchi model, a plot of % drug release versus square root of time.

$Q=K_2t½$

4) **Peppa's and Korsemeyer equation:** The mechanism of drug release can evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation.

$Mt/M\alpha = K.tn$

5) **Hixson-Crowell release model:** Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion.

$(100\text{-}Qt)^{1/3} = 1001/3 – KHC._t$

Where

Q = the amount of drug released at time t,

K = zero order rate constant,

K1 = first order rate constant,

K2 = Higuchi rateconstant,

Mt = amount of drug released at time t and

Mα= the amount released at time α

Mt/Mα = the fraction of drug released at time t,

k = kinetic constant and

n = diffusion exponent.

F) Material Used for the PDDS[16]

Sr. no	Material
Water insoluble polymer	Calcium pectinate, calcium alginate, glutaraldehyde guar gum, pectin, alginic acid, vegetable gum.
Disintegrant	Crosspovidone, microcrystalline starch, SSG, L-HPC. Sodium carboxymethyl cellulose,
Hardness enhancer	MCC, starch, PVP, L-HPC, HPMC.
Lubricants	Talc, magnesium state
Glident	Fumed silica
Binder	Ethyl cellulose, PVP, pectin.
Film former	HPMC, povidone, hydroxyl ethylcellulose, polycrylate, polymethylcrylate, polymethyl/ethylacrylate.
Hydrophobic polymer	Carbomer, Carnauba wax, Glyceryl palmitosterate, Hydrogenated castor oil, Microcrystalline wax, Polacriline potassium, Polymethacrylate, Stearic acid
Hydrophilic polymer	Caboxymethyalcellulose, Guar gum, Hydroxyethylcellulose, Hydroxypropylcellulose, methylcellulose, HPMC.

Some polymer which relese drug at different condition as follows

Sr.no.	Stimulus	polymer	Drug relese
	pH	cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose, N, N-dimethylaminoethyl methacrylate, chitosan, polyol	Insulin
2	Electric field	Poly(methacrylic acid) (PMA)	Pilocarpine and raffinose
3	Glucose concentration	Poly(methacrylic acid-co-butyl methacrylate)	Insulin
4	Temperature	Layer of Chitosan Pluronic on PLGA microparticles	Indomethacin
5	Morphine concentration	Methyl vinyl ether-Co-anhydride maleic copolymer	Naltrexone
6	Urea concentration	Methyl vinyl ehter-Co-anhydride maleic copolymer	Hydrocortisone

MARKETED PRODUCT[16-33]

No	API	Brand	Technology	manufacturer	material used	Use
1	**amoxicillin**	Moxatag	PULSYS®	Fera Pharmaceuticals, Advancis Pharmaceutical Corp., USA MiddleBrook's	PEG, waxes, paraffin, acrylic acid, ethylcellulose, eudragit, cellulose acetate pthalate, talc, HPC, HPMC, Dibutyl Sebacate, Magnesium stearate,	Antibiotic
2	Nifedipine	Procardia	TIMERx(R), OROS	Mylan, Pfizer Laboratories Div Pfizer Inc	cellulose acetate, hydroxypropyl cellulose HPMC, magnesium stearate, polyethylene glycol, ferric oxide red, sodium chloride, titanium dioxide	Hypertension (high blood pressure) and angina (chest pain).
3	Methylphenidate	Ritalin LA		Novartis	Polyvinylpyrrolidone, sugar spheres, Opadry Clear, ethylcellulose, Aquacoat® ECD-30, dibutyl sebacate	CNS stimulant
4	Paliperidone	Invega	OROS®	Janssen Pharmaceuticals	Polyethylene oxide, sodium chloride, HPMC, steric acid, HPC, Povidone, anhydrous ethyl alcohol, cellulose acetate, PEG, Triethyl citrate, Acetone, Water, Eudragit FS 30D, Talc, Acryl Eze, 0.1 N HCL.	Antipsychotic

5	Oxymorphone	Opana ER	TIMERx Technology,	Penwest Pharmaceuticals, Endo Pharm	Microcrystalline cellulose, sodium steryl fumerate, opadry, Locust Bean, Xanthan Gum, Calcium Sulfate Dihydrate, Ethyl cellulose, Alcohol	Analgesic
6	Verapamil HCL	covera HS	OROS®	pfizer inc.	Butylated hydroxy tolune, cellulose acetate, HPC, HPMC, magnesium Sterate, PEG, Polysorbate 80, povidone, sodium chloride, titanium dioxide, ferrous ferric oxide. Alluminium oxide, FD & c Red 30	calcium channel blocker
7	Prednisone	rays	Geoclock technology	Horizon Pharma	Lactose, Polyvinyl pyrrolidone, Sodium carboxymethyl cellulose, Magnesium stearate, Silicon dioxide, Dibasic calcium, Glyceryl Behenate, Yellow Ferric Oxide, Magnesium stearate	anti-inflammatory, antimmunosuppressant
8	Gliclazide	Diamicron MR	hydrophyllic matrix	Ranbaxy	PVP, DCP dehydrate, HPMC K100LV, HPMC K4M CR, Aerosil, Magnesium sterate,	Antidiabetic
9	Methylphenidate	Concerta	OROS®	Janssen Pharmaceuticals	hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.	CNS stimulant
10	Tulobuterol	**Hokunalin®**		Abott Laboratories	Dibutylhydroxytoluene, Oleic acid Styrene isoprene, styrene block copolymer Saturated alicyclic hydrocarbon, Polybutene Liquid paraffin	Bronchodilator
11	Famotidine	Pepcid	physico chemical modification of the API	Salix Pharms, Valeant Pharms North, : Lupin Ltd, Alembic Pharma, :	Cellulose Acetate, HPC, Eudragit E 100, Ethyl Cellulose/, HEC, Sorbitol, Cellulose Triacetate,	H2 receptor Antagonist

				Wockhardt	Polyvinylpyrrolidone, Calcium Carbonate, , Colloidal SiO2, Peppermint Flavor, Magnesium Stearate, Dextrates, Mannitol, Microcrystalline Cellulose, Aspartame, Corn Starch, Dye/Pigment	
12	Diltiazem	**Cardizem LA**		Valeant Intl, Actavis Labs Fl Inc		calcium channel blocker.
13	Simvastatin,	Zoco	physico chemical modification of the API	Aurobindo Pharma, Dr Reddys Labs Inc, Hetero Labs Ltd Iii, Merck, Ranbaxy.		anticholesterol
14	Propranolol	InnoPran XL	Diffucaps TM	Reliant Pharmaceuticals	sugar spheres, ethylcellulose, povidone, hypromellose phthalate, diethyl pthalate, hypromellose, polyethylene glycol, gelatin, titanium dioxide and black iron oxide.	Beta Blocker
15	verapamil HCL	Verelan®Pm	CODAS	Schwarz Pharma	D&C Red #28, FD & C Blue #1, FD&C red #40, fumaric acid, gelatin, povidone, shellac, silicon dioxide, sodium lauryl sulfate, starch, sugar spheres, talc, and titanium dioxide.	calcium channel blocker
16	Theophylline	Uniphyllin		Nile pharma	hydroxy ethyl cellulose, povidne K25, cetosteryl alcohol, PEG-6000, talc, magnesium sterate, water	Bronchodilators

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