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RECENT WORK ON CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT:
Controlled drug delivery system is the better than in comparison to conventional drug delivery. The goal of controlled drug delivery is to maintain the plasma concentration of drug. It follows the zero order kinetics of drug release. The rational of this drug delivery system is to reduce the dose frequency, reduce the side effect and dose of drug. In this system the drug release at predetermined rate at a fixed period of time. The fabrication of controlled drug delivery system has been always a challenge to formulation scientist due to their inability to retain and localize the system at targeted areas of the gastrointestinal tract.

Keywords: Controlled drug delivery, Osmotic controlled release, Osmotic Pump, Gastrointestinal tract.

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INTRODUCTION

In past 30 years, as the expenditure and difficulties included in marketing new drug delivery system have increased so greater research has been focused on fabrication of controlled release drug delivery system. The conventional drug delivery systems like tablet, capsules, suspensions, ointments, liquids and aerosols are widely used, mainly conventional drug are effective but some drugs are unstable, toxic, narrow therapeutic ranges. To overcome these problems controlled drug delivery system were introduced in past years.

The objectives of fabrication of controlled release drug delivery system is to decrease the dosing frequency of drug, reduce the dose and administering the uniform drug delivery, so controlled release formulation is a dosage form that release the drug for predetermined rate for a specific time period. It assists good control of plasma drug level. The hydrophilic polymers are widely used in fabrication of controlled release formulation. The ideal characteristics of dosage form is to assist proper amount of drug at specific time period, it is target oriented drug delivery system. In recent years empirical and technical advancement have been made in the design and fabrication of rate controlled drug delivery system by combat physiological adversities, such as short gastric residence time and unpredictable gastric emptying times[1-3].

Ideal characteristics of controlled drug delivery system

a) Comfortable for patient
b) Capable for achieving high drug loading
c) Safe from accidental release
d) Ease to remove
e) Ease of fabrication

Advantages of controlled drug delivery system[2,4]

a) Patient compliance
b) Reduce the dosing frequency of drug
c) Eliminate the local side effect
d) Maintain the plasma drug levels
e) Increases the bioavailability of drug
f) Enhancement of activity duration for short half-life drugs
g) Improves efficacy in treatment

Disadvantages of controlled drug delivery system[3]

a) Reduce the systemic availability of drug in comparison to immediate release
b) Dose dumping
c) Poor in vitro- in vivo correlation

d) Poor systemic availability
e) High cost of formulation

CONTROLLED RELEASE MECHANISMS OF DRUG

It is broadly divided into following categories:

1. Dissolution controlled release
a) Matrix dissolution control
b) Reservoir dissolution control
2. Diffusion controlled release
a) Matrix diffusion control
b) Reservoir diffusion control
3. Osmotic controlled release
4. Ion exchange release

1. Dissolution control release[5]

In this formulation, the dissolution rate of drug depends on polymer nature. In this formulation first of all coating of polymer is dissolved then the drug is available for dissolution. The dissolution is also depends on thickness of coating materials and its composition.

Matrix dissolution control: In this system the slow water dissolving carrier generally used. The drug is compress with dissolving carriers and forms a matrix type structures. The highly water soluble drug are fabricated by using slowly dissolving polymers for controlled the release of drug.

Reservoir dissolution control: In this system, the drug particles are coated with slowly dissolving materials such as cellulose derivatives, polyethylene glycols, waxes etc. by microencapsulation techniques for better release of drug.

2. Diffusion controlled release[6]

In this system, water insoluble polymers are generally using for control the flow of water and continue release of drug. It is divided in two categories:

Matrix diffusion control release: This system basically depends on diffusion process. In this system the drug are dispersed in polymer solution to prepare a homogeneous matrix system, diffusion occurs when the drug release for the matrix system to the external environment.

Reservoir diffusion control: In this system, the water insoluble polymers are used for control the release of drug. The drug particles are coated with polymers by microencapsulation techniques. It is rate controlled process.

3. Osmotic controlled release[7-10]

In this method the controlling release rate of drug is depends on osmotic agents between inside and outside the compartment. This system basically depends on osmotic pressure and provide zero order release kinetics of hydrophilic drug, Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. The advantages of this formulation is that the release unaltered by the environment of the GIT. The osmotic controlled drug delivery system can be divided into following categories.

1. Single chamber osmotic pump
a) Elementary osmotic pump
2. Multi chamber osmotic pump
a) Push pull osmotic pump
b) Osmotic pump with non expanding second chamber
3. Specific types
a) Controlled porosity osmotic pump
b) Monolithic osmotic system
c) Osmotic bursiting osmotic pump
d) Multi particulate delayed release system
e) Liquid oral osmotic system

4. Ion exchange release

These are various types of resins used in pharmaceuticals application. These resins are generally water insoluble polymers carrying ionisable functional groups. In tablet formulation it is used as a disintegrant because of its swelling properties. In this system, the drug bound to cross linked resins polymers, when it is ingested in GIT it show release of drug in controlled way.

WORK DONE ON CONTROLLED DRUG DELIVERY: The work and patent on controlled drug delivery is described in table 1 and table 2.

Table No 1: Work done on controlled drug delivery system

S. No	Author	Drug	Method/Polymer	Inference	Ref.
1.	Chao Qin et. al. (2014)	Metformin HCl	Osmotic pump tablet	Follow zero order release rate and excellent bioavalability of drug	11
2.	P. Motugatla et. al. (2013)	Losartan potassium	Direct compression method	Better controlled release and improved bioavailability	12
3.	G. Ramana et. al. (2012)	Ambroxol HCl	Melt granulation method	Controlled release of drug	13
4.	T.V. Rao et. al. (2012)	Losartan potassium	Wet granulation method	The drug release follow zero-order kinetics and found diffusion controlled mechanism	14
5.	R.L.C. Sasidhar et. al. (2012)	Losartan potassium	Direct compession method	Efficiently control the drug release	15

				for prolonged period of time.	
6.	N.R. Shamma et. al.(2011)	Betahistidine	Matrix tablet	Release in controlled manner	16
7.	R.U. Muthumanikander et. al. (2011)	Losartan potassium	Wet granulation method	The optimized formulation obeys the first order release kinetics	17
8.	S.T. Prajapati et. al. (2011)	Zolpidem tartrate	Melt granulation method	Drug release in the controlled menner	18
9.	H. Doddayya et. al. (2011)	Venlafaxine HCl	Direct compression method	Follow non-fickian diffusion model	19
10.	M. Azharuddin et. al. (2011)	Losartan potassium	Direct compression method	Better controlled release for a period of 24 hrs.	20
11.	D.B. Raju et. al. (2010)	Losartan potassium	Direct compression method	Successfully formulated controlled release drug delivery system	21
12.	J. Emami et. al. (2008)	Flutamide	Direct compression method	Follow first order kinetics	22
13.	G.S. et. al. (2008)	Zidovudine	Matrix tablet	Drug release in controlled manner	23
14.	J. Shahla et. al. (2006)	Glipizide	Hydroxy propyl methyl cellulose	Drug release in zero order kinetics manner	24
15.	H.K. Raslan et. al. (2006)	Theophylline	Direct compression method	Follow first order eguation and Hixson crowell cuberoot law	25
16.	N.V. Rahman et. al. (2005)	Diltiazem HCl	Matrix tablet	Release in controlled manner	26
17.	C.W. Vendruscolo et. al. (2005)	Theophylline	Direct compressiom method	Drug release in zero order kinetics manner	27
18.	D. Prabakaran et. al. (2003)	Diltiazem HCl	Wet granulation method	Reduce the release rate of drug	28
19.	A.B. Silvina et. al. (2002)	Diclofenac	Wet granulation process	Follow zero order release kinetics	29
20.	S. Takka et. al. (2001)	Propranolol	Direct compression method	Drug release in controlled manner	30

Table No 2: Patents on controlled drug delivery

S. No	Author	Drug	Method/polymer	Inference	Ref.
1.	J. S. Christopher et. al. (2013)	Theophylline	Direct compression method	Drug release in controlled manner	31
2.	J. Quingwai et. al. (2012)	Active drug	Osmotic pump tablet	Follow zero order kinetics	32
3.	G. Zong et. al. (2012)	Paliperidone	Providone, carbomer, hydroxypropyl cellulose	Increase drug release rate at early stage and keeps a constant drug release rate at later stage	33
4.	S. K. Kulkarni et. al. (2012)	Milnacipran	Hydoxypropyl methyl cellulose	Control release of the drug over prolonged periods of time	34
5.	G. A. Sereno et. al. (2011)	Losartan potassium	Direct compression method	Increase gastric retention time of drug	35
6.	C. Umit et. al. (2011)	Pregablin	Wet granulation method	Retained in the stomach and follow controlled release	36
7.	B. J. Lee et. al. (2011)	Aceclofenac	Hydroxypropyl methyl cellulose, carbomer, sodium hydrogen carbonate	Release of drug in controlled manner	37
8.	P. Nilbon et. al. (2010)	Valproic acid	Water insoluble polymer and enteric polymer	Drug release in controlled way	38
9.	T. Nghiem et. al. (2010)	Active substance	Ethyl cellulose, Hydroxyethyl cellulose	Invention provides pseudo first order, first order and zero order release kinetics	39
10.	N. B. Dharmadhikari et. al. (2010)	Metaprolol	Hydroxypropyl methyl cellulose	Provide a technique of decreasing the risk of alcohol induced dose dumping	40
11.	S. P. Pilgaonkar et. al. (2008)	Verapamil HCl	Dry granulation method	Providing reduce initial burst release	41
12.	D. John et. al. (2008)	Losartan potassium	Dry blend process	Release of drug in controlled manner	42

13.	G. J. Young et. al. (2008)	Thiazides or angiotensin II receptors	Hydrophilic polymer	Follow zero order release kinetics	43
14.	F. Vanderbist et. al. (2007)	Active substance	Malt granulation	Provide prolonged release of drug and optimal floating properties	44
15.	J. K. Mandal et. al. (2007)	Oxcarbazepine	Direct compression	Drug release in controlled manner	45
16.	C. Xiu Xiu et. al. (2006)	Metformin	Hydroxypropyl cellulose	Provide controlled or sustained release of drug	46
17.	P. C. Gary et. al. (2005)	Oxytocin	Hydrophilic polymer	Increase half life and provides sustained release	47
18.	M. F. Befumo et. al. (2004)	Zafirlukast	Hydroxypropyl methyl cellulose	Drug release in controlled manner	48
19.	M. Kumar et. al. (2003)	Clarithromycin or tinidazole	Hydroxypropyl cellulose	Drug release in controlled manner	49
20.	M. Chawla et. al. (2003)	Metformin	Non-ionic and anionic hydrophilic polymers	Follow zero order release kinetics	50
21.	Q. Yihong et. al. (2002)	Divalprox sodium	Hydroxypropyl methyl cellulose	Follow zero order release pattern	51
22.	E. King et. al. (2000)	Cgmp PDE-5 inhibitors	Hydroxypropyl methyl cellulose	Prevention of sexual dysfunction	52
23.	A. M. Mehta et. al (1999)	Nifedipine	Water pearmeable polymer	Controlled release of drug	53
24.	C. M. Chih et. al. (1998)	Diltiazem HCl	Polyvinyl pyrrolidone	Release of drug in controlled manner	54
25.	C. Chih Ming et. al. (1996)	Active drug	Granulation method	Controlled release of drug	55
26.	C. Chih Ming et. al. (1995)	Active drug	Hydroxypropyl methyl cellulose	Follow zero order release pattern	56
27.	A. R. Baichwal et. al. (1992)	Verapamil	Hydroxypropyl methyl cellulose	Controlled release of verapamil in GIT	57
28.	T. C. George et. al. (1992)	Active drug	Direct compression method	Controlled release of drug	58
29.	M. T. Decrosta et. al. (1985)	Captopril	Hydroxypropyl methyl cellulose	Release of drug in controlled manner	59

EVALUATION PARAMETERS[60]

1. Pre compression parameters[61,62]

a) Bulk density: It is ratio of mass of powder and volume of powder. Bulk density depends on particle size of ingredients, its distribution and shape of particle. Bulk density mathematically expressed in (gm/cc)

$$Db = M/Vo$$

Where, Db = Bulk density (gm/cc)
M = is the mass of powder (gm)
Vo = is the bulk volume of powder (cc)

b) Tapped density: Powder was placed in 100ml clean measuring cylinder. The cylinder was then tapped 100 times from constant height. It is expressed in gm/cc

$$Dt = M/Vo$$

Where, Dt = tapped density (gm/cc)
M = is the mass of powder
Vt = is the tapped volume of powder

c) Compressibility index: It is determine by carr's index

carr's index (%) = b = (V/b)×100

Table No 3: Flow properties according to carr's index

S. No	Carr's index	Flow properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to passable
4	23-30	Poor
5	33-38	Very poor
6	>40	Very very poor

d) Hausner ratio: It is the ratio of tapped density and bulk density

Table No 4: Flow properties according to hausner ratio

Hausner ratio	Flow properties
< 1.25	Good
>1.25	Poor

e) Angle of repose: It is defined as the maximum angle between the surface of pile of the powder and the horizontal plane. The angle of repose was then calculated using the formula

$$\tan \theta = h/r$$

$\theta = \tan^{-1}(h/r)$
h = height of pile
r = radius of the base of the pile

Table No 5: Flow properties according to angle of repose

S. No	Angle of repose	Flow properties
1	<25	Excellent
2	25- 30	Good
3	30- 40	Passable
4	>40	Very poor

f) Total porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of powder blend (The space occupied by the powder exclusive of space greater than the intermolecular space, V)

$$\text{Porosity (\%)} = \text{Vbulk-V/Vbulk} \times 100$$

2) Post compression parameters:

a) Thickness and diameters: The thickness and diameter was measured using by vernier callipers in mm.

b) Hardness: The Monsanto hardness tester was used to determine the hardness of tablets. Hardness was expressed in kg/cm^2.

c) Friability: Friability of tablet was tested by USP friabilator. First of all tablets are weighed and placed in friabilator for 100 revolution. The % friability was calculated by

$$F = (Wi\text{-}Wf)/ Wi \times 100$$

Where, Wi = initial weight
Wf = final weight

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

Table No 6: Weight variation limit

S. No	Average weight of tablet (mg)	Maximum difference
1	130 or less	10 %
2	130 – 324	7.5%
3	324 or more	5%

PD = (Wavg- Wi)/ Wi×100
PD = Percentage deviation

e) DSC study: The physicochemical composition of the drug and the used excipients were tested by differential scanning calorimetric analysis. DSC thermograms of the drug alone and drug excipients physical mixture were derived from a DSC with a thermal analysis data station system, plotter interface, and computer.

f) Drug content: In this test accurately weight amount of powder was dissolve in water and filtered. After that the absorbance was measured at fixed wavelength by UV spectrophotometer.

g) In- Vitro drug release study: The in vitro dissolution study was done by using USP dissolution apparatus type II. The drug was placed in dissolution media and then after some specific time interval sample withdrawn and media replaced. During the dissolution study each sample was analyzed using UV spectrophotometer.

CONCLUSION

The controlled drug delivery system is better than compare conventional drug delivery system because in CDDS the release rate of drug is control and specific time period. It is maintaining the therapeutic level of drug in blood plasma; it is reducing the dose and its frequency. For these discussions, we can assure that the CDDS increasing the efficiency of the dose and reducing the dosing frequency. The release models with major application and best describing drug release phenomena are in general the zero order model, higuchi model, first order model and korsemeyer-peppas model. Further, it can be added that the physicochemical properties of the drug as well as polymer and the drug to polymer ratio govern the release of drug from the formulation and thus, modify the release kinetics accordingly. There are several evaluation parameters used in controlled drug delivery system such as DSC study, drug release profile, IR spectroscopy, friability, etc. The release of drug in controlled drug delivery system is at predetermined rate.

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