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(54) **Title**: USE OF PHARMACEUTICAL COMPOSITION FOR GASTRORETENTIVE SUSTAINED AND PULSATILE DRUG DELIVERY SYSTEM

(57) **Abstract**: The invention discloses a gastroretentive drug delivery system comprising a drug in the core and coated with a coating of a pH sensitive polymer, P such that the polymer P has formula P(AxByCz), wherein A is selected from MMA and EMA, B is selected from BMA and EHM and C is 4-VP and $x = 1\text{-}60\ \%$, $y = 30\text{-}92\ \%$ and $z = 4\text{-}11\ \%$, all values expressed as % w/w, such that $x+y+z=100$, said polymer swells at $pH < 3.5$, and neither swells nor dissolves at $pH > 3.5$. The gastroretentive system of the invention can release the drug in both sustained and pulsatile manners.

USE OF PHARMACEUTICAL COMPOSITION FOR GASTRORETENTIVE SUSTAINED AND PULSATILE DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

The invention relates to a use of pharmaceutical composition for gastroretentive drug delivery system comprises a core of drug and gas generating agent wherein said core is coated with a novel pH sensitive polymer, for improving the absorption of drug. More particularly, the release of the drug from the gastroretentive drug delivery system is in sustained or pulsatile manner.

BACKGROUND OF THE INVENTION

Site specific drug delivery systems are the systems that target the drug release in the part of gastrointestinal tract from where the drug is absorbed specifically. Owing to differences in solubility and / or instability in different regions of gastrointestinal tract as a result of presence of enzymes, environmental pH or interaction with endogenous components such as bile salts, drugs exhibit limited absorption window. Drugs like riboflavin (Kagan et al, 2006), metformin (Stepensky et al, 2001 and Marathe et al, 2000), ciprofloxacin (Harder et al, 1990) and valacyclovir (Kagan and Hoffman, 2008) are preferably absorbed from stomach or proximal intestine. Gastric retention of dosage forms is one of the ways to address limited absorption window of the drugs. Gastric retention is achieved by variety of mechanisms like floating systems, mucoadhesive systems, expanding systems and high density systems.

Floating systems are the most successful mechanism of gastroretention among these technologies. Most of the gastroretentive systems available in the market are based on floating mechanism (Singh and Kim, 2000). Floating systems for metformin (Glumetza) and ciprofloxacin HCl (Proquin XR) are developed by Depomed Inc. Floating systems should possess certain properties to fabricate a successful product. These properties include floating characteristics and drug release control through matrices. Also the delivery system should guarantee its removal from the stomach after complete drug release. Depomed patented floating systems (US patent 6723340) based on physical mixture of PEO and HPMC. These systems swell and control drug release for 6-8 h and continue to swell thereafter, whereas the drug delivery system should be cleared from the stomach immediately after complete drug release.

Numerous research and patent publications disclose the gastroretentive dosage forms. For e.g. US20060134054 discloses a novel pH sensitive polymer which exhibits pH dependant swelling/dissolution behavior useful for taste masking of bitter drugs and also for the gastric delivery of the drugs. The said polymer comprises a hydrophobic monomer polymerized along with a basic monomer or a hydrophobic monomer polymerized along with a basic monomer and a hydrophilic monomer. Although MMA and VP as components in instant invention are similar to the composition to US 20060134054, the difference is in the third component, i.e. HEMA in the US patent that causes dissolution of drug within 45 minutes, whereas here it is replaced by a hydrophobic, rubbery monomer, unlike HEMA which is a hydrophilic, but glassy monomer. This replacement, which leads to the desired floating and buoyancy time as exemplified herein is surprising and would not be obvious to a person skilled in the art.

However the objective here is to develop a polymer that dissolves and releases drug completely in 45 minutes, specifically for drugs whose availability in intestine being poor, drug should be released in stomach and that too immediately.

Menjoge and Kulkarni (2007) disclose a self-associated cationic polymer (NREP) containing methyl methacrylate (MMA), 2-hydroxy ethylmethacrylate (HEMA) and 4-vinyl pyridine (4-VP) (*Biomacromolecules*, 2007, 8 (2), pp 532–542) which performs identical function. Clearly these polymers are not suitable for sustained / pulsatile release in stomach.

US5651985 describes a physical preparation to achieve extended residence times in the stomach in the form of tablets, capsules, grains and/or pellets. Pellet, comprising: (I) at least one pharmacologically active compound, (II) at least one pharmacologically acceptable substance, (III) polyvinylpyrrolidone, (IV) a methacrylic acid polymer having an acidic number between 100 and 1,200 mg of KOH/g of polymer, and (V) optionally a gas-forming additive, the polymers (III) and (IV) being present in the form of a homogeneous mixture being present in 30-90 % by weight of the composition, the weight ratio of (III):(IV) ranging from 80:20 to 95:5, and the composition in dry compressed state being able to absorb many times its weight of acidic water thereby to form a highly swollen gel of high mechanical and dimensional stability capable of prolonged release of the pharmacologically active compound.

Another article **by Basak**, et al. (Pharmazie (2007), 62(2), 145-148. ISSN: 0031-7144) discloses the formulation of Metformin hydrochloride as a floating (buoyant) matrix tablet using a gas generating agent (sodium bicarbonate) and a gel forming hydrophilic polymer (hydroxypropyl methylcellulose). The formulation was optimized on the basis of floating ability and in vitro drug release.

Further, research article by Krogel and Bodmeier (1999) relates to development and evaluation of floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. For the floating system, a polymer coating with a high elongation value and high water- and low CO_2 permeabilities was selected (Eudragit RL/acetyltributyl citrate 20 %, wt./wt.) in order to initiate the effervescent reaction and the floating process rapidly, while for the pulsatile DDS, a weak, semipermeable film, which ruptured after a certain lag time was reported (Et cellulose/dibutyl sebacate 20%, wt./wt.).

Sustained release formulations are not efficient in treating the diseases, especially diseases with chronological pathophysiology, for which, pulsatile drug delivery is beneficial. Pharmaceutical agents for treatment of conditions like hypertension, asthma and arthritis exhibit symptoms based on circadian rhythm. Therefore there is need to deliver drugs to treat such conditions after a time lag when such symptoms are at peak. Further, the continuous exposure of drug as obtained with standard sustained release of drug to microbes causes them to go into dormant stage. Therefore, there is need to develop gastroretentive drug delivery systems which release drug in pulsatile manner as well as in sustained manner.

Presently available gastroretentive pulsatile systems exhibit broadening of the release profiles and there is no clear separation between two pulses.

OBJECTS OF THE INVENTION

Main objective of the present invention is to provide a gastroretentive drug delivery system with clear separation between the two pulses, for improving the effectiveness of drug which comprises a core of drug and gas generating agent wherein said core is coated with a novel pH sensitive polymer.

Another objective of the present invention is to provide a gastroretentive drug delivery system with sustained release for improving the effectiveness of drug with the use of novel pH sensitive polymer.

SUMMARY OF THE INVENTION

Accordingly, present invention provides use of the pharmaceutical composition as gastroretentive drug delivery system comprising active pharmaceutical ingredient and coated with a pH sensitive polymer of formula I

$$P(AxByCz)$$

Formula I

wherein A is selected from methyl methacrylate (MMA)and Ethyl methacrylate (EMA), B is selected from n-butyl methacrylate (BMA) and 2-ethylhexyl methacrylate (EHM) and C is 4-vinyl pyridine (4-VP) and $x = 1\text{-}60$ %, $y = 30\text{-}92$ % and $z = 4\text{-}11$ %, all values expressed as % w/w, such that the sum of x, y and z is 100, said polymer swells at $pH < 3.5$, and neither swells nor dissolves at $pH > 3.5$; optionally along with pharmaceutically acceptable excipients.

In an embodiment of the present invention, active pharmaceutical ingredient is selected from the group consisting of antibacterial agent, non-steroidal anti-inflammatory agent (NSAID), cardiovascular agent, hypoglycemic agent, antiasthmatic agent, antiarthritic agent and such like.

In another embodiment of the present invention, antibacterial agent is selected from the group consisting of ciprofloxacin HCl, ofloxacin, amoxicillin, cephalexin monohydrate preferably ciprofloxacin HCl; NSAID is selected from ketoprofen, acetaminophen and ibuprofen preferably acetaminophen; cardiovascular agent is selected from verapamil HCl, propranolol HCl, captopril and diltiazem HCl, preferably verapamil HCl; hypoglycemic agent is selected from metformin HCl, and glipizide; antiasthmatic drug is selected from theophylline, Montelukast sodium and salbutamol and antiarthritic drug is selected from acetaminophen, methotrexate and prednisolone.

In yet another embodiment of the present invention, pharmaceutically acceptable excipients are selected from the group consisting of filler, binder and lubricant.

In yet another embodiment of the present invention, filler is selected from group consisting of microcrystalline cellulose, lactose and mannitol.

In yet another embodiment of the present invention, binder is selected from polyvinyl pyrrolidone 30 or hydroxypropylmethyl cellulose 5 cps.

In yet another embodiment of the present invention, said lubricant is selected from magnesium stearate and talc.

In yet another embodiment of the present invention, the active pharmaceutical ingredient is present in the core in the range of 25 % to 70 % w/w.

In yet another embodiment of the present invention, polymer coating is in the range of 3 to 20 % w/w of the coated core.

In yet another embodiment of the present invention, drug to polymer ratio is in the range of 1:0.06 to 1: 0.3.

In yet another embodiment of the present invention, said gastroretentive drug delivery system is in the form of sustained gastroretentive drug delivery system.

In yet another embodiment of the present invention, said sustained gastroretentive drug delivery system has buoyancy time in the range of 1 min to 3 h.

In yet another embodiment of the present invention, said sustained gastroretentive drug delivery system has floating time in the range of 2 to 24 h.

In yet another embodiment of the present invention, the drug release is sustained from 0.5 h to 24 h.

In yet another embodiment of the present invention, said gastroretentive drug delivery system is in the form of pulsatile gastroretentive drug delivery system.

In yet another embodiment of the present invention, in pulsatile gastroretentive drug delivery system, core containing the active pharmaceutical ingredient is sequentially coated by more than one pH sensitive polymer.

In yet another embodiment of the present invention, in pulsatile gastroretentive drug delivery system thickness of the individual layer in pulsatile gastroretentive drug delivery system is in the range of 0.5 mm and 0.9 mm.

In yet another embodiment of the present invention, in pulsatile gastroretentive drug delivery system, the pulses are obtained between 0.5 and 9 h.

In yet another embodiment of the present invention, in pulsatile gastroretentive drug delivery system, drug is released for a period of 1.5 h to 7 h after time lag of 1 to 7 h.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Cumulative CIP release from composition of example 32

Figure 2: The timed release of CIP from composition of example 32

Figure 3: Cumulative CIP release from composition of example 33

Figure 4: The timed release of CIP from composition of example 33

Figure 5: Drug release from timed gastroretentive tablets of example 35

Figure 6: Cumulative drug release profile for tablets of example 36

Figure 7: Cumulative CIP release of example 39

Figure 8: CIP release rate of example 39

Figure 9: Cumulative CIP release of example 40

Figure 10: CIP release rate of example 40

Figure 11: Cumulative CIP release of example 41

DETAILED DESCRIPTION OF THE INVENTION

Active pharmaceutical ingredient of the present invention will mean and include bulk active in medicine; active ingredient (AI), and drug. Different abbreviations used in the present invention are CIP: Ciprofloxacin hydrochloride, VER: Verapamil hydrochloride; TPH: Theophylline; ACP: Acetaminophen; MMA: Methyl methacrylate; BMA: n-butyl methacrylate; VP: 4-vinyl pyridine; EMA: Ethyl methacrylate; EHM: 2-ethylhexyl methacrylate; MET: Metformin hydrochloride; CFL: Cephalexin monohydrate

The choice of components of the polymer of the invention A, B and C are done in such a way, such that sum of x, y and z is 100. It may be kindly noted here that after the selection of x and y for components A and B respectively, selection of z for C is done such that $x+y+z=100$.

For example, If $x=48$, $y=40$, then z will be 12, which is within 4-17%. 2. If say $y=92\%$, then x and z will be chosen between the ranges provided such that $x+y+z=100$ and the polymer should swellable at $pH < 3.5$ and neither swell nor dissolve at $pH > 3.5$.

The pulsatile formulations of the present invention show separation between pulses and hence exhibits better in vivo results than those exhibited by earlier systems.

The present invention describes a gastroretentive drug delivery system for improving the effectiveness of drug which comprises a core of drug and gas generating agent wherein said core is coated with a novel pH sensitive polymer.

The present invention provides a gastroretentive drug delivery system, wherein the drug is released in sustained or pulsatile manner.

The present invention addresses both the above issues i) by encapsulating drugs in polymers which release the drug after predetermined lag time, ii) by a judicious combination of dosage form prepared in i).

The gastroretentive drug delivery system comprises pH sensitive polymer such that the polymer P is swellable at pH < 3.5 and neither swells nor dissolves at pH > 3.5 having formula P(AxByCz), wherein A is selected from MMA and EMA, B is selected from BMA and EHM and C is 4-VP and $x = 1\text{-}60$ %, $y = 26\text{-}92$ % and $z = 4\text{-}17$ %, all values expressed as % w/w, such that $x+y+z=100$.

The present inventors have surprisingly found that it is possible to obtain gastroretentive drug delivery system by using polymer P(AxByCz) in both sustained as well as in pulsatile manner by employing the monomer content in a specified range.

The sustained gastroretentive drug delivery system comprises pH sensitive polymer such that the polymer P has formula P(AxByCz), wherein A is selected from MMA and EMA, B is selected from BMA and EHM and C is 4-VP and $x = 1\text{-}60$ %, $y = 30\text{-}92$ % and $z = 4\text{-}11$ %, all values expressed as % w/w, such that $x+y+z=100$, swells at pH < 3.5, and neither swells nor dissolves at pH > 3.5.

The pH sensitive polymer is synthesized by conventional techniques known in the art selected from bulk, solution, emulsion or dispersion polymerization, preferably by bulk or solution polymerization. The drug to polymer ratio in the present invention is in the range 1:0.06 to 1: 0.3.

The gastroretentive drug delivery system of present invention comprises core coated with a pH sensitive polymer, wherein polymer coating is 3 % to 20 % w/w of the coated core.

The active pharmaceutical ingredient of the present invention may be selected from antibacterial agent, non-steroidal anti-inflammatory agent (NSAID), cardiovascular agent, hypoglycemic agent, antiasthmatic agent, antiarthritic agent and such like. The active pharmaceutical ingredient is present in the core in the range of 25 % to 70 % w/w.

Suitable antibacterial agent is selected from ciprofloxacin HCl, ofloxacin, amoxicillin, cephalexin monohydrate preferably ciprofloxacin HCl; NSAID is selected from ketoprofen, acetaminophen and ibuprofen preferably acetaminophen; cardiovascular agent is selected from verapamil HCl, propranolol HCl, captopril and diltiazem HCl, preferably verapamil HCl; hypoglycemic agent is selected from metformin HCl, and glipizide; antiasthmatic drug is selected from theophylline, Montelukast sodium and salbutamol and antiarthritic drug is selected from acetaminophen, methotrexate and prednisolone.

The invention describes a sustained gastroretentive drug delivery system for improving the effectiveness of active pharmaceutical ingredient, which comprises a core of drug and gas generating agent, wherein said core is coated with pH sensitive polymer P such that the polymer P is swellable at pH < 3.5 and has formula P(AxByCz), wherein A is selected from MMA and EMA, B is selected from BMA and EHM and C is 4-VP and wherein x = 1-60 %, y = 30-92 % and z = 4-11 %, all values expressed as % w/w, such that x+y+z=100, swells at pH < 3.5, and neither swells nor dissolves at pH > 3.5 along with pharmaceutically acceptable excipients.

The invention describes a pulsatile gastroretentive drug delivery system for improving the effectiveness of active pharmaceutical ingredient which comprises a core of drug and gas generating agent wherein said core is coated with pH sensitive polymer P such that the polymer P is swellable at pH < 3.5 and has formula P(AxByCz), wherein A is selected from MMA and EMA, B is selected from BMA and EHM and C is 4-VP and x = 1-60 %, y = 30-92 % and z = 4-11 %, all values expressed as % w/w, such that x+y+z=100, swells at pH < 3.5, and neither swells nor dissolves at pH > 3.5, along with pharmaceutically acceptable excipients.

The pulsatile gastroretentive drug delivery system having the core containing the drug is sequentially coated by more than one pH sensitive polymer. The thickness of the individual layer in pulsatile gastroretentive drug delivery system varies between 0.5 mm and 0.9 mm.

The pharmaceutically acceptable excipients of the present invention are selected from group comprising filler, binder and lubricant.

Suitable filler is selected from group consisting of microcrystalline cellulose, lactose and mannitol; suitable binder is selected from polyvinyl pyrrolidone 30 and hydroxypropyl methyl cellulose 5 cps and suitable lubricant is selected from magnesium stearate and talc.

The sustained gastroretentive drug delivery system of the present invention has a buoyancy time in the range 1 min to 2 h and floating time in the range 2 h to 24 h and releases the drug over a period of 2 h to 24 h.

In pulsatile gastroretentive drug delivery system, the drug is released as a pulse between 0.5 h and 9 h. The drug is released after a time lag of 1 h to 7 h or for a period of 1.5 h to 7 h after time lag of 1 to 7 h.

The coating layer remains intact during the release of the drug.

Tablet cores were prepared by direct compression method. All the ingredients were weighed, mixed together and compressed into 13 mm diameter tablets. Tablet cores were coated with a solution of pH sensitive polymer till desired weight gain was achieved.

The dissolution experiment was carried out in 900 ml of 0.1 N hydrochloric acid using USP type II apparatus at 37±0.5° C at 50 rpm. The drug release was monitored by UV spectroscopy at 277, 233, 278, 262, 270 and 244 nm for CIP, MET, VER, CFL, TPH and ACP respectively. The buoyancy time (BT) was taken as the time required to float the tablet and total floating time (FT) and the time over which drug was released was also noted as release time (RT).

EXAMPLES

Following examples are given by way of illustration therefore should not be construed to limit the scope of the invention.

EXAMPLES FOR SUSTAINED GASTRORETENTIVE DRUG DELIVERY SYSTEM

Example 1

a) Preparation of tablet core: The CIP tablet was prepared as per composition table 1.

Table 1: Composition of CIP tablet

Ingredient	Weight (mg)
CIP	250.0
Lactose monohydrate	69.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 48:41:11 respectively. The weight of coated tablet was 525 mg.

c) Dissolution study of coated tablet

The dissolution of coated tablet was monitored. The BT and FT were 38 min and 4 h respectively. The dissolution profile of coated tablet is described in table 2.

Table 2: CIP release profile from coated tablet

Time (h)	0	1	2	3	4
% drug release	0	16	35	56	99

Example 2

The CIP tablet was prepared as described in example 1. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing

MMA, BMA and VP in weight ratio 36:53:11 respectively. The weight of coated tablet was 525 mg.

The dissolution of coated tablet was monitored. The BT and FT of tablet were 2 h and 5 h respectively. The dissolution profile of coated tablet is described in table 3.

Table 3: CIP release profile from coated tablet

Time (h)	0	1	2	3	4	5
% drug release	0	0	10	76	90	99

Example 3

The CIP tablet was prepared as described in example 1. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 25:65:10 respectively. The weight of coated tablet was 525 mg. The dissolution of coated tablet was monitored. BT and FT were 1 h and 7 h respectively. The dissolution profile of coated tablet is described in table 4.

Table 4: CIP release profile from coated tablet

Time (h)	0	1	2	3	4	5	6	7
% drug release	0	7	23	33	54	74	90	99

Example 4

The CIP tablet was prepared as described in example 1. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 16:74:10 respectively. The weight of the coated tablet was 525 mg. The dissolution of coated tablet was monitored. The BT and FT were 49 min and 5 h respectively. The dissolution profile of coated tablet is described in table 5.

Table 5: CIP release profile from coated tablet

Time (h)	0	1	2	3	4	5
% drug release	0	22	43	70	92	99

Example 5

The CIP tablet was prepared as described in example 1. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 8:82:10 respectively. The weight of coated tablet was 530 mg. The dissolution of coated tablet was monitored. The BT and FT were 57 min and 10 h respectively. The dissolution profile of coated tablet is described in table 6.

Table 6: CIP release profile from coated tablet

Time (h)	0	1	2	3	4	5	6	7	8	9	10
% drug release	0	17	35	38	45	50	56	60	68	74	81

Example 6

The acetaminophen tablet was prepared as per composition in table 7.

Table 7: Composition of ACP tablet

Ingredient	Weight (mg)
Acetaminophen	100.0
Lactose monohydrate	220.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	75.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 8:82:10 respectively. The weight of coated tablet was 515 mg. The dissolution of coated tablet was monitored. The BT and FT were 58 min and 24 h respectively. The dissolution profile of coated tablet is shown in table 8.

Table 8: ACP release profile from coated tablet

Time (h)	0	2	4	6	8	10	12	14	16	22	24
% drug release	0	39	56	64	75	77	78	80	85	87	89

Example 16

The CIP tablet was prepared as described in example 1. The tablet was coated with 8 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 18:78:4 respectively. The weight of coated tablet was 525 mg. The dissolution of coated tablet was monitored. The BT and FT were 178 min and 24 h respectively. The dissolution profile of coated tablet is described in table 21.

Table 21: CIP release profile from coated tablet

Time (h)	0	2	4	6	8	10	12	14	16	18	20	22	24
% drug release	0	3	5	8	11	16	22	31	44	60	76	88	92

Example 17

a) Preparation of tablet core

The CIP tablet was prepared as described in example 9. The tablet was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing EMA, BMA and VP in weight ratio 11:81:8 respectively. The weight of coated tablet was 550 mg. The dissolution of coated tablet was monitored. The BT and FT were 76 min and 18 h respectively. The dissolution profile of coated tablet is described in table 22.

Table 22: CIP release profile from coated tablet

Time (h)	0	0.5	1	2	4	6	8	12	14	18
% drug release	0	1	13	45	50	63	69	77	82	88

Example 18

The CIP tablet was prepared as described in example 9. The tablet was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing EMA, BMA and VP in weight ratio 18:75:7 respectively. The weight of coated tablet was 535 mg. The dissolution of coated tablet was monitored. The BT and FT were 25 min and 3 h respectively. The dissolution profile of coated tablet is described in table 23.

Table 23: CIP release profile from coated tablet

Time (h)	0	0.5	1	2	3
% drug release	0	46	66	85	100

Example 19

The CIP tablet was prepared as described in example 9. The tablet was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing EMA, BMA and VP in weight ratio 47:44:9 respectively. The weight of coated tablet was 530 mg. The dissolution of coated tablet was monitored. The BT and FT were 36 min and 2 h respectively. The dissolution profile of coated tablet is described in table 24.

Table 24: CIP release profile from coated tablet

Time (h)	0	0.5	1	2
% drug release	0	26	86	99

Example 20

The VER tablet was prepared as described in example 14. The tablet was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing EMA, BMA and VP in weight ratio 11:81:8 respectively. The weight of the coated tablet was 540 mg. The dissolution of coated tablet was monitored. The BT and FT were 27 min and 4 h respectively. The dissolution profile of coated tablet is described in table 25.

Table 25: VER release profile from coated tablet

Time (h)	0	0.5	1	2	3	4
% drug release	0	8	25	45	80	99

Example 21

The VER tablet was prepared as described in example 14. The tablet was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing EMA, BMA and VP in weight ratio 11:81:8 respectively. The weight of coated tablet was 560 mg. The dissolution of coated tablet was monitored. The BT and FT were 52 min and 9 h respectively. The dissolution profile of coated tablet is described in table 26.

Table 26: VER release profile from coated tablet

Time (h)	0	0.5	1	2	3	4
% drug release	0	3	7	38	84	98

Example 22

The CIP tablet was prepared as described in example 1. The tablet was coated with 8 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, EHM and VP in weight ratio 16:74:10 respectively. The weight of coated tablet was 525 mg. The dissolution of coated tablet was monitored. The BT and FT were 20 min and 4 h respectively. The dissolution profile of coated tablet is described in table 27.

Table 27: CIP release profile from coated tablet

Time (h)	0	1	2	3	4
% drug release	0	13	84	89	91

EXAMPLES FOR PULSATILE GASTRORETENTIVE DRUG DELIVERY

Example 24

a) Preparation of tablet core

The CIP tablet was prepared as per composition in table 30.

Table 30: Composition of CIP tablet

Ingredient	Weight (mg)
Ciprofloxacin hydrochloride	250.0
Lactose monohydrate	69.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0

Total	500.0

c) Dissolution study of tablet core

The dissolution profile of tablet core is described in table 31.

Table 31: CIP release profile from tablet

Time (h)	0	0.5
% drug release	0	99

Example 25

The CIP tablet was prepared as described in example 24. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 57:26:17 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 18 min, 2.5 h and 1 h respectively. The dissolution profile of coated tablet is described in table 32.

Table 32: CIP release profile from coated CIP tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5
% drug release	0	4	15	28	83	98

Example 26

The CIP tablet was prepared as described in example 24. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 45:38:17 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 31 min, 5.5 h and 1.5 h respectively. The dissolution profile of coated tablet is described in table 33.

Table 33: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
% drug release	0	0	3	7	21	24	29	32	47	65	75	98

Example 27

The CIP tablet was prepared as described in example 24. The tablet was coated with 10% w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 22:62:16 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 47 min, 6 h and 3 h respectively. The dissolution profile of coated tablet is described in table 34.

Table 34: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
% drug release	0	0	1	6	6	6	11	23	38	56	83	94

Example 28

The CIP tablet was prepared as described in example 24. The tablet was coated with 10% w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 15:70:15 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 56 min, 12 h and 6 h respectively. The dissolution profile of coated tablet is described in table 35.

Table 35: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6
% drug release	0	0	0	0	0	0	0	2	2	4	5	7	1

contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0	11.5	12.0
% drug release	14	20	28	41	49	60	63	68	74	83	87	92

Example 29

The CIP tablet was prepared as described in example 24. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 135 min, 12 h and 7 h respectively. The dissolution profile of coated tablet is described in table 36.

Table 36: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6
% drug release	0	0	0	0	0	0	0	0	1	1	2	3	

contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0	11.5	12.0
% drug release	7	9	13	18	26	35	44	52	59	65	72	74

Example 30

The CIP tablet was prepared as described in example 24. The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing BMA and VP in weight ratio 85:15 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 58 min, 12 h and 5 h respectively. The dissolution profile of coated tablet is described in table 37.

Table 37: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
% drug release	0	0	0	0	0	1	2	3	5	8	12	19

contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	11.0	12.0
% drug release	30	36	47	55	66	70	74	80	85	89

Example 31

The CIP tablet was prepared as per composition in table 38.

Table 38: Composition of CIP tablet

Ingredient	Weight (mg)
Ciprofloxacin hydrochloride	200.0
Lactose monohydrate	70.0
Sodium bicarbonate	130.0
Citric acid, anhydrous	95.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 10 % w/v solution in chloroform using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 22:62:16 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 1.5, 5 and 3.5 h respectively. The dissolution profile of coated tablet is described in table 39.

Table 39: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
% drug release	0	0	0	0	3	3	8	12	27	81	100

Example 32

The coated CIP tablets as described in example 24, 25 and 27 were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablets was monitored. The cumulative drug release profile is described Table 40. The CIP release of example 9 is shown in figure 1 and 2.

Table 40: Cumulative CIP release profile

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6
% drug release	0	33	35	40	44	63	69	73	78	84	93	97	9

Example 33

The CIP tablets as described in example 24, 25 and 31 were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablet was monitored. The cumulative drug release profile is described Table 41. The CIP release of example 10 is shown in figure 3 and 4.

Table 41: Cumulative CIP release profile for example 33

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
% drug release	0	35	36	40	46	65	72	73	77	93	99

Example 34

a) Preparation of tablet core

The CIP tablet was prepared as per composition in table 42.

Table 42: Composition of CIP tablet

Ingredient	Weight (mg)
CIP	320.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	75.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 8 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, EHM and VP in weight ratio 13:74:14 respectively. The weight of coated tablet was 530 mg. The dissolution of tablet was monitored. The BT and FT were 10 min and 1 h respectively. The dissolution profile of coated tablet is described in table 43.

Table 43: CIP release profile from coated tablet

Time (h)	0	0.5	1.0
% drug release	0	90	99

Example 35

a) Preparation of tablet core:

The tablet cores for two drugs, CIP and TPH were prepared as per compositions in table 44.

Table 44: Compositions of drug cores

Name of excipient	Tablet 1	Tablet 2
CIP	250	0
TPH	0	250
Lactose	69	69
Sodium bicarbonate	100	100
Citric acid	76	76
Mg stearate	5	5
Total	500	500

b) Tablet coating

The tablet 2 was coated with 10 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The composition of tablets is described in table 45.

Table 45: Composition of tablets

Ingredient	Weight (mg)	
	CIP tablet	TPH tablet
Core tablet weight	500.0	500.0
pH sensitive polymer	0.0	75.0
Total	500.0	575.0

c) Dissolution study of coated tablet

The dissolution experiment was carried out by combining two tablets. The dissolution profile of coated tablets is described in table 46 and figure 5.

Table 46: Drug release profile from time gastroretentive tablets

Time (h)	0	0.5	1.0	2.0	3.0	4.0	4.5	5.0	5.5
% CIP release	0	100	-	-	-	-	-	-	-
% TPH release	0	0	0	1	6	10	14	17	19

Contd...

Time (h)	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0
% CIP release	-	-	-	-	-	-	-	-	-
% TPH release	23	31	43	50	60	76	90	98	100

Example 36

a) Preparation of tablet core:

The tablet cores as per compositions in table 47 were prepared.

Table 47: Compositions of drug cores

Name of excipient	Tablet 1	Tablet 2
CIP	250	0

TPH	0	125
Lactose	69	194
Sodium bicarbonate	100	100
Citric acid	76	76
Mg stearate	5	5
Total	500	500

b) Tablet coating

Tablet 2 was coated with 8 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The composition of tablets is described in table 48.

c) Dissolution study of coated tablet:

The dissolution experiment was carried out by combining two tablets. The dissolution profile of tablets is described in table 49 and figure 6.

Table 48: Composition of tablet

Ingredient	Weight (mg)	
	CIP tablet	TPH tablet
Core tablet weight	500.0	500.0
pH sensitive polymer	-	70.0
Total	500.0	570.0

Table 49: Drug release profile from timed gastroretentive tablets

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0
% CIP release	0	98	-	-	-	-	-
% TPH release	0	0	1	1	1	3	7

Contd...

Time (h)	3.5	4.0	4.5	5.0	5.5	6.0
% CIP release	-	-	-	-	-	-
% TPH release	17	23	27	46	70	98

Example 37

a) Preparation of tablet core:

The CIP tablet was prepared as per composition in table 50.

Table 50: Composition of CIP tablet

Ingredient	Weight (mg)
CIP	125.0
Lactose monohydrate	194.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0
Total	500.0

c) Dissolution study of tablet core

The dissolution of tablet was monitored. The dissolution profile of tablet core is described in table 51.

Table 51: CIP release profile from tablet

Time (h)	0	0.5
% drug release	0	100

Example 38

a) Preparation of tablet core

The CIP tablet was prepared as described in example 37.

b) Tablet coating

The tablet was coated with 12 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 57:26:17 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 0.25 , 2.5 and 1 h respectively. The dissolution profile of coated tablet is described in table 52.

Table 52: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5
% drug release	0	0	18	39	92	99

Example 39

The CIP tablets as described in example 37 and 31 were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablets was monitored. The cumulative drug release profile is described table 53 and figure 7 and 8.

Table 53: Cumulative CIP release from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	3.0	3.5	4.0	4.5	5.0	5.5	6.0
% drug release	0	38	38	38	41	45	47	58	85	96	98	98

Example 40

The CIP tablets as described in example 37 and 29 were prepared and taken to prepare timed gastroretentive delivery system. The dissolution of tablets was monitored. The cumulative drug release profile is described table 54 and figures 9 and 10.

Table 54: Cumulative CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
% drug release	0	33	33	34	35	36	37	37	38	38	40	41	42

Contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0
% drug release	44	48	51	64	68	74	79	81

Example 41

The CIP tablets as described in examples 38 and 28 were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablet was monitored. The cumulative drug release profile is described table 55 and figures 11 and 12.

Table 55: Cumulative CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
Drug release (%)	0	0	6	13	31	33	33	34	34	34	35	35	36	37

Contd...

Time (h)	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0	11.5	12.0	12.5	13.0
Drug release (%)	39	40	44	49	64	71	76	81	85	89	92	94	97

Example 42

The CIP tablets as described in examples 38 and 31 were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablets was monitored. The cumulative drug release profile is described table 56 and figures 13 and 14.

Table 56: Cumulative CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
Drug release (%)	0	0	6	12	39	41	44	46	55	77	86	88

Example 43

The CIP tablets as described in example 37 and 29 (with 5% w/w coating level) were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablet was monitored. The cumulative drug release profile is described in table 57 and figures 15 and 16. The BT and FT for coated tablet was 51 min and 10.5 h respectively.

Table 57: Cumulative CIP release profile from tablets

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
Drug release (%)	0	33	47	56	57	57	60	63	68	70	74	75	76

Contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5
Drug release (%)	78	78	78	82	87	91	93	99	99

Example 44

The CIP tablets as described in example 37 and 29 (10 % w/w coating level) were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution of tablet was monitored . The cumulative drug release profile is described table 58 and figures 17 and 18. The BT and FT for coated tablet was 71 min and 5.5 h respectively.

Table 58: Cumulative CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
Drug release (%)	0	33	33	33	34	37	45	63	77	87	97	100

Example 45

The CIP tablets as described in example 38 and a coated tablet from example 29 but with drug content 350 mg, coated with 20% w/w built up were prepared and taken to prepare pulsatile gastroretentive drug delivery system. The dissolution study of tablets was done. The cumulative drug release profile is described table 59 and figures 19 and 20.

Table 59: Cumulative CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
Drug release (%)	0	26	26	26	26	26	26	26	29	29	33	35	40

Contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0	11.5	12.0
Drug release (%)	43	47	51	56	65	70	72	77	80	84	85	86

Example 46

a) Preparation of tablet core:

The CIP tablet was prepared as described in example 24.

b) Tablet coating:

The tablet was coated sequentially first with 8 % w/v solution in dichloromethane using a pH sensitive polymer 1 containing MMA, BMA and VP in weight ratio 57:26:17 and then with 8 % w/v solution in dichloromethane using a pH sensitive polymer 2 containing MMA, BMA and VP in weight ratio 22:62:16. The composition of coated tablets is described in table 60.

Table 60: Composition of CIP coated tablet

Ingredient	Weight (mg)
Ciprofloxacin HCl tablet	500.0
pH sensitive polymer 1	65.0
pH sensitive polymer 2	68.0
Total	633.0

c) Dissolution study of coated tablet

The dissolution of coated tablet was monitored. The BT, FT and lag time were 2 h, 4 h and 1.75 h respectively. The dissolution profile of coated tablet is described in table 61.

Table 61: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
% drug release	0	0	0	1	23	74	93	98	100

Example 47

The CIP tablet was prepared as described in example 24. The tablet was coated sequentially first with 8 % w/v solution in dichloromethane using a pH sensitive polymer 1 containing MMA, BMA and VP in weight ratio 57:26:17 and then with 8 % w/v solution in dichloromethane using a pH sensitive polymer 2 containing MMA, BMA and VP in weight ratio 22:62:16. The composition of coated tablets is described in table 62.

Table 62: Composition of CIP coated tablet

Ingredient	Weight (mg)
Ciprofloxacin HCl tablet	500.0
pH sensitive polymer 1	95.0
pH sensitive polymer 2	107.0
Total	702.0

The dissolution of coated tablet was monitored. The BT, FT and lag time were 1 h 49 min, 5 h and 2.25 h respectively. The dissolution profile of coated tablet is described in table 63.

Table 63: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
% drug release	0	0	0	0	0	15	37	62	88	98	100

Example 48

The CIP tablet was prepared as described in example 24. The tablet was coated sequentially first with 10 % w/v solution in dichloromethane using a pH sensitive polymer 1 containing MMA, BMA and VP in weight ratio 57:26:17 and then with 10 % w/v solution in chloroform using a pH sensitive polymer 2 containing MMA, BMA and VP in weight ratio 15:70:15. The composition of coated tablets is described in table 64.

Table 64: Composition of CIP coated tablet

Ingredient	Weight (mg)
Ciprofloxacin HCl tablet	500.0
pH sensitive polymer 1	85.0
pH sensitive polymer 2	88.0
Total	673.0

The BT, FT and lag time were 2.75, 6 and 4 h respectively. The dissolution profile of coated tablet is described in table 65.

Table 65: CIP release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
% drug release	0	0	0	0	0	0	0	3	11	39	63	96	100

Example 49

a) Preparation of tablet core

The VER tablet was prepared as per composition in table 66.

Table 66: Composition of VER tablet

Ingredient	Weight (mg)
VER	320.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	75.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated sequentially first with 12 % w/v solution in dichloromethane using a pH sensitive polymer 1 containing MMA, BMA and VP in weight ratio 57:26:17 and then with 10 % w/v solution in chloroform using a pH sensitive polymer 2 containing MMA, BMA and VP in weight ratio 15:70:15. The composition of coated tablets is described in table 67.

Table 67: Composition of coated VER tablet

Ingredient	Weight (mg)

VER tablet	500.0
pH sensitive polymer 1	85.0
pH sensitive polymer 2	88.0
Total	673.0

c) Dissolution study of coated tablet

The dissolution experiment was carried out on two coated tablets. The BT, FT and lag time were 0, 3.5 and 2 h respectively. The dissolution profile of coated tablet is described in table 68.

Table 68: VER release profile from coated tablet

Time (h)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
% drug release	0	1	1	2	8	31	94	100

Example 50

a) Preparation of tablet core:

The Theophylline tablet was prepared as per composition in table 69.

Table 69: Composition of TPH tablet

Ingredient	Weight (mg)
TPH	125.0
Lactose monohydrate	194.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The TPH tablet was coated with 8 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The weight of the coated tablet was 575 mg.

c) Dissolution study of coated tablet:

The dissolution experiment was carried out on coated tablet. The BT, FT and lag time were 78 min, 7 h and 3 h respectively. The dissolution profile of coated tablet is described in table 70.

Table 70: TPH release profile from coated tablet

Time (h)	0	1.0	2.0	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0
% drug release	0	0	3	13	18	22	32	45	58	74	93	100

Example 51

a) Preparation of tablet core:

ACP tablet was prepared as per composition in table 71:

Table 71: Composition of ACP tablet

Ingredient	Weight (mg)
Acetaminophen	250.0
Lactose monohydrate	69.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 12 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The weight of coated tablet was 575 mg. The dissolution of tablet was monitored. The BT, FT and lag time were 4.5, 13 and 6.5 h respectively. The dissolution profile of coated tablet is described in table 72.

Table 72: ACP release profile from coated tablet

Time (h)	0	1.0	2.0	3.0	3.5	4.0	4.5	5.0	5.5	6.0
% drug release	0	0	2	2	2	2	3	5	5	8

Contd...

Time (h)	6.5	7.0	7.5	8.0	8.5	9.0	10.0	11.0	12.0	13.0
% drug release	12	14	18	20	26	33	50	60	85	97

Example 52

a) Preparation of tablet core

ACP tablet was prepared as per composition in table 73.

Table 73: Composition of tablet

Ingredient	Weight (mg)
ACP	125.0
Lactose monohydrate	194.0
Sodium bicarbonate	100.0
Citric acid, anhydrous	76.0
Magnesium stearate	5.0
Total	500.0

b) Tablet coating

The tablet was coated with 12 % w/v solution in dichloromethane using a pH sensitive polymer containing MMA, BMA and VP in weight ratio 11:74:15 respectively. The weight of coated tablet was 575 mg. The dissolution study of coated tablet was done. The BT, FT and lag time were 4.25, 10 and 6 h respectively. The dissolution profile of coated tablet is described in table 74.

Table 74: ACP release profile from coated tablet

Time (h)	0	1.0	2.0	3.0	3.5	4.0	4.5	5.	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.5	9.5	10.0
% drug release	0	1	1	1	1	2	5	7	9	10	14	15	15	46	61	78	88	100

We claim

1. The use of the pharmaceutical composition as gastroretentive drug delivery system comprising active pharmaceutical ingredient coated with a pH sensitive polymer of formula I

   P(AxByCz)

   Formula I

   wherein A is selected from methyl methacrylate (MMA)and Ethyl methacrylate (EMA), B is selected from n-butyl methacrylate (BMA) and 2-ethylhexyl methacrylate (EHM) and C is 4-vinyl pyridine (4-VP) and $x = 1\text{-}60$ %, $y = 30\text{-}92$ % and $z = 4\text{-}11$ %, all values expressed as % w/w, such that the sum of x, y and z is 100 and said polymer swelling at $pH < 3.5$, and neither swelling nor dissolving at $pH > 3.5$; optionally along with pharmaceutically acceptable excipients.
2. The use as claimed in claim 1, wherein active pharmaceutical ingredient is selected from the group consisting of antibacterial agent, non-steroidal anti-inflammatory agent (NSAID), cardiovascular agent, hypoglycemic agent, antiasthmatic agent, antiarthritic agent and such like.
3. The use as claimed in claim 2, wherein antibacterial agent is selected from the group consisting of ciprofloxacin HCl, ofloxacin, amoxicillin, cephalexin monohydrate preferably ciprofloxacin HCl; NSAID is selected from ketoprofen, acetaminophen and ibuprofen preferably acetaminophen; cardiovascular agent is selected from verapamil HCl, propranolol HCl, captopril and diltiazem HCl, preferably verapamil HCl; hypoglycemic agent is selected from metformin HCl, and glipizide; antiasthmatic drug is selected from theophylline, Montelukast sodium and salbutamol and antiarthritic drug is selected from acetaminophen, methotrexate and prednisolone.
4. The use as claimed in claim 1, wherein pharmaceutically acceptable excipients are selected from the group consisting of filler, binder and lubricant.
5. The use as claimed in claim 4, wherein said filler is selected from group consisting of microcrystalline cellulose, lactose and mannitol.
6. The use as claimed in claim 4, wherein binder is selected from polyvinyl pyrrolidone 30 or hydroxypropylmethyl cellulose 5 cps.
7. The use as claimed in claim 4, wherein said lubricant is selected from magnesium stearate and talc.

8. The use as claimed in claim 1, wherein the active pharmaceutical ingredient is present in the core in the range of 25 % to 70 % w/w.
9. The use as claimed in claim 1, wherein polymer coating is in the range of 3 to 20 % w/w of the coated core.
10. The use as claimed in claim 1, wherein drug to polymer ratio is in the range of 1:0.06 to 1: 0.3.
11. The use as claimed in claim 1, wherein said gastroretentive drug delivery system is in the form of sustained gastroretentive drug delivery system.
12. The use as claimed in claim 11, wherein said sustained gastroretentive drug delivery system has buoyancy time in the range of 1 min to 3 h.
13. The use as claimed in claim 11, wherein said sustained gastroretentive drug delivery system has floating time in the range of 2 to 24 h.
14. The use as claimed in claim 11, wherein the drug release is sustained from 0.5 h to 24 h.
15. The use as claimed in claim 1, wherein said gastroretentive drug delivery system is in the form of pulsatile gastroretentive drug delivery system.
16. The use as claimed in claim 15, wherein said pulsatile gastroretentive drug delivery system, core containing the active pharmaceutical ingredient is sequentially coated by more than one pH sensitive polymer.
17. The use as claimed in claim 15, wherein thickness of the individual layer in pulsatile gastroretentive drug delivery system is in the range of 0.5 mm and 0.9 mm.
18. The use as claimed in claim 15, wherein said pulsatile gastroretentive drug delivery system the pulses are obtained between 0.5 and 9 h.
19. The use as claimed in claim 15, wherein drug is released for a period of 1.5 h to 7 h after time lag of 1 to 7 h.

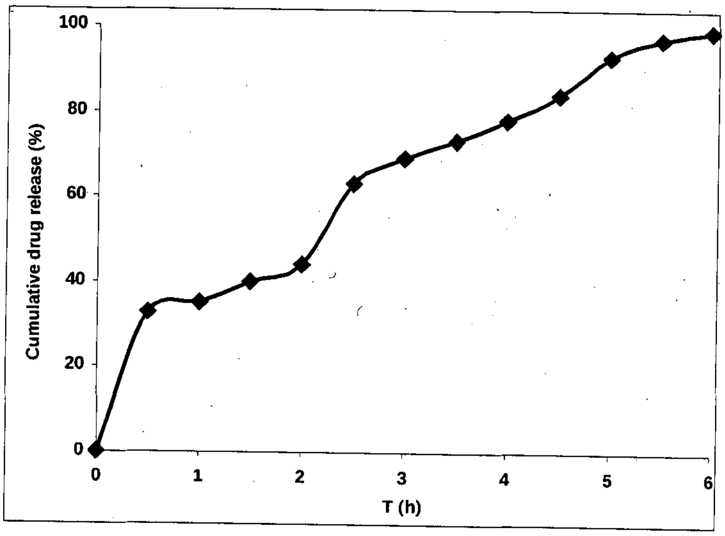
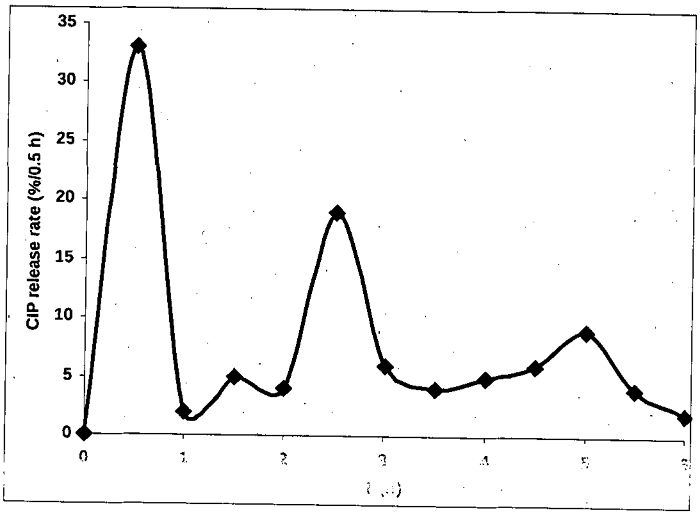


Figure 1



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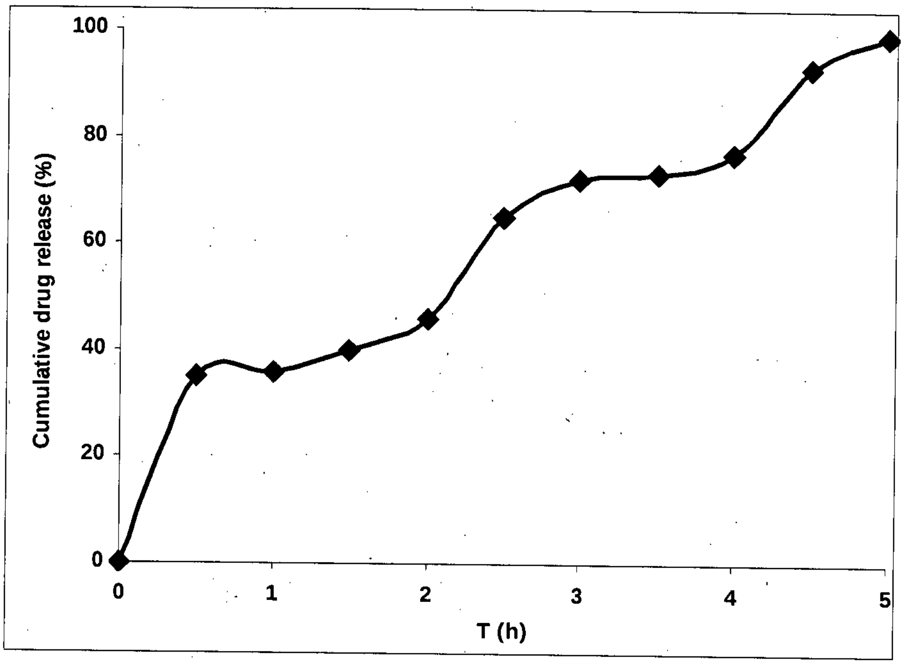

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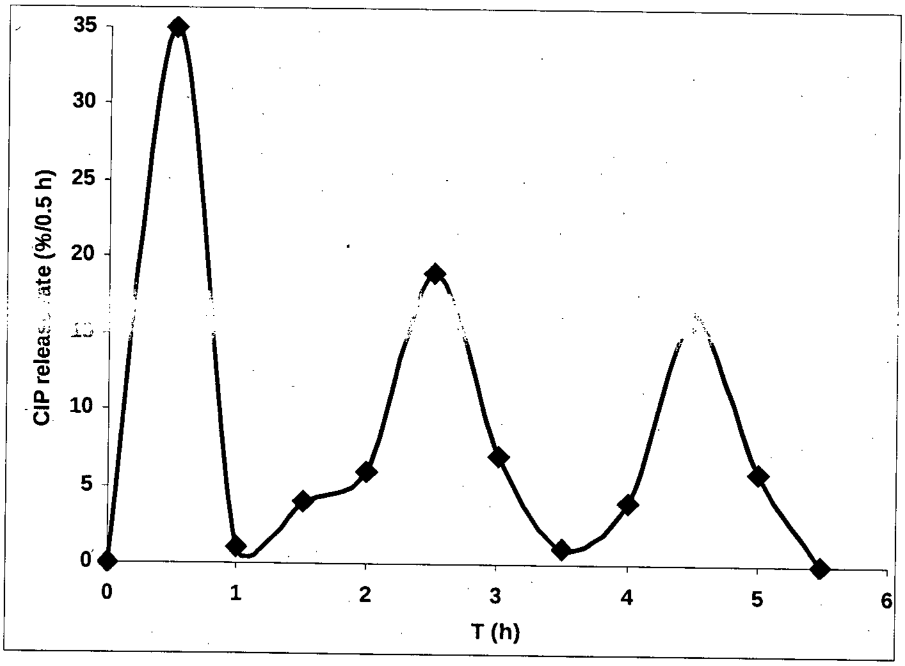

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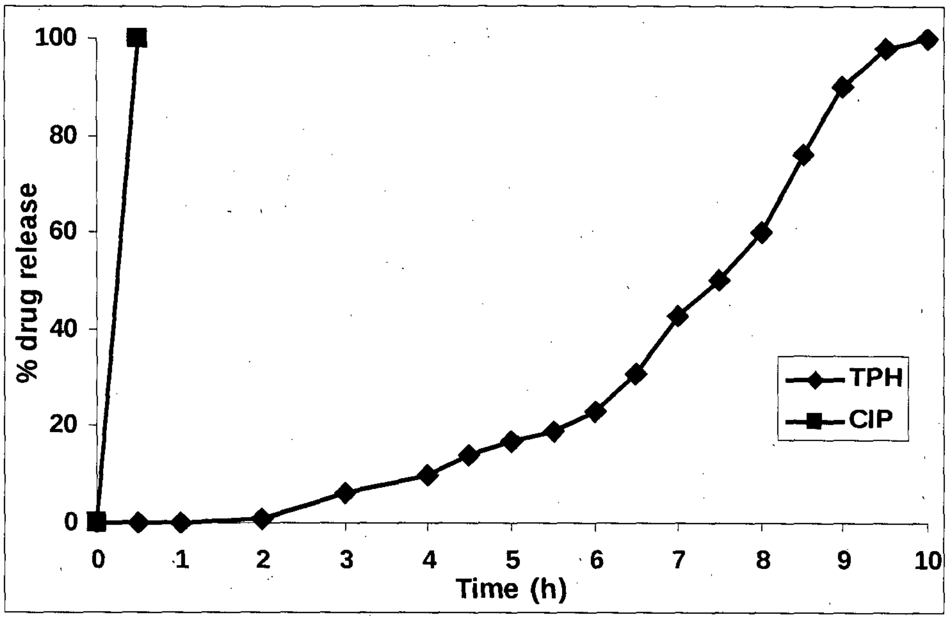

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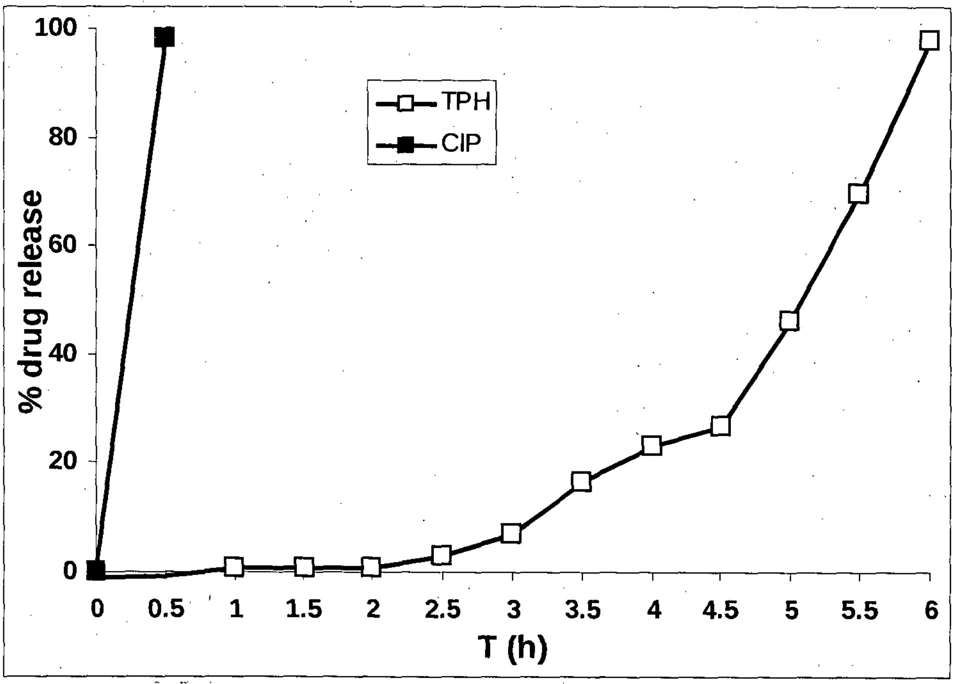

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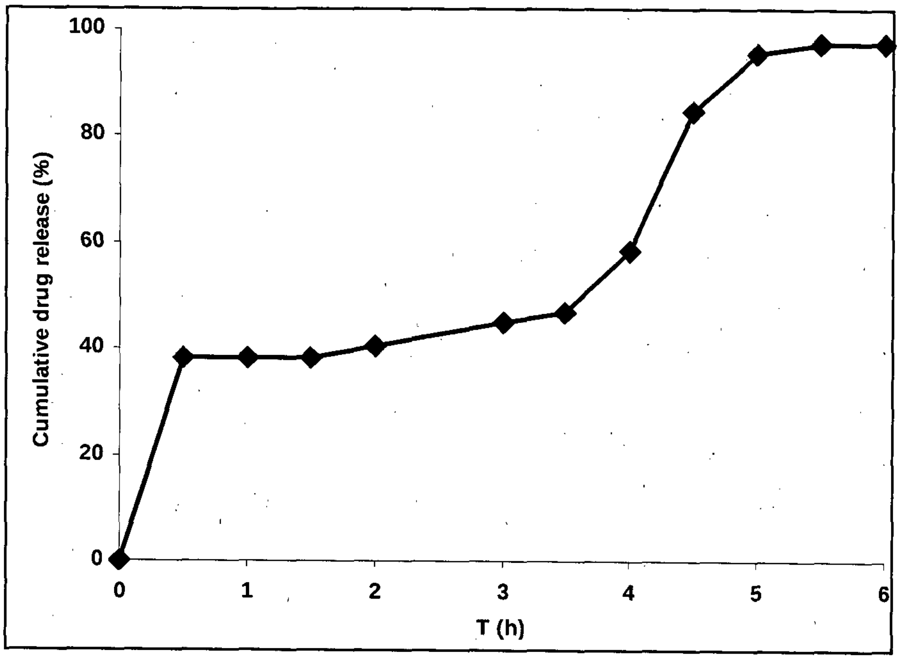

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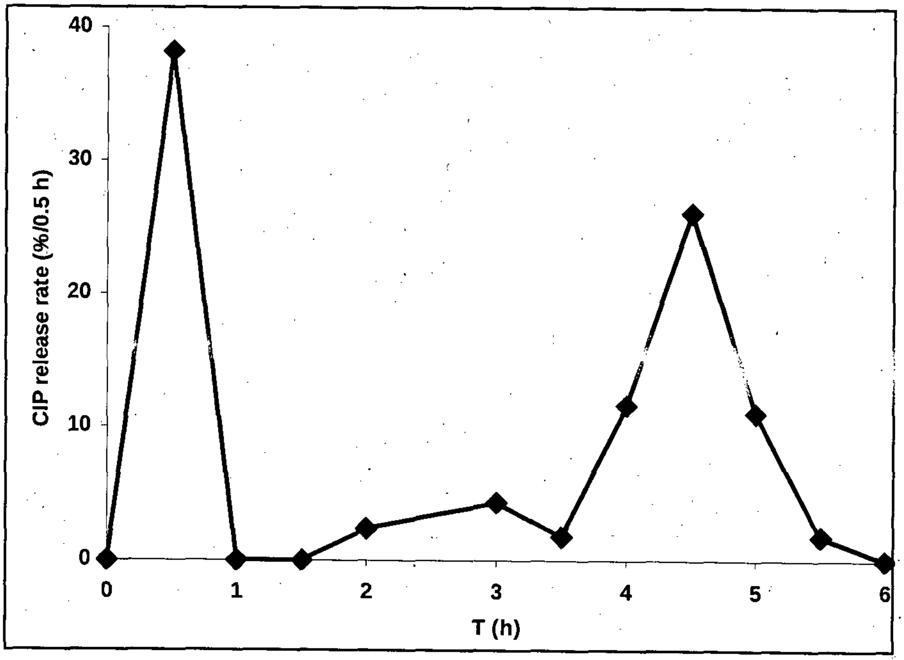

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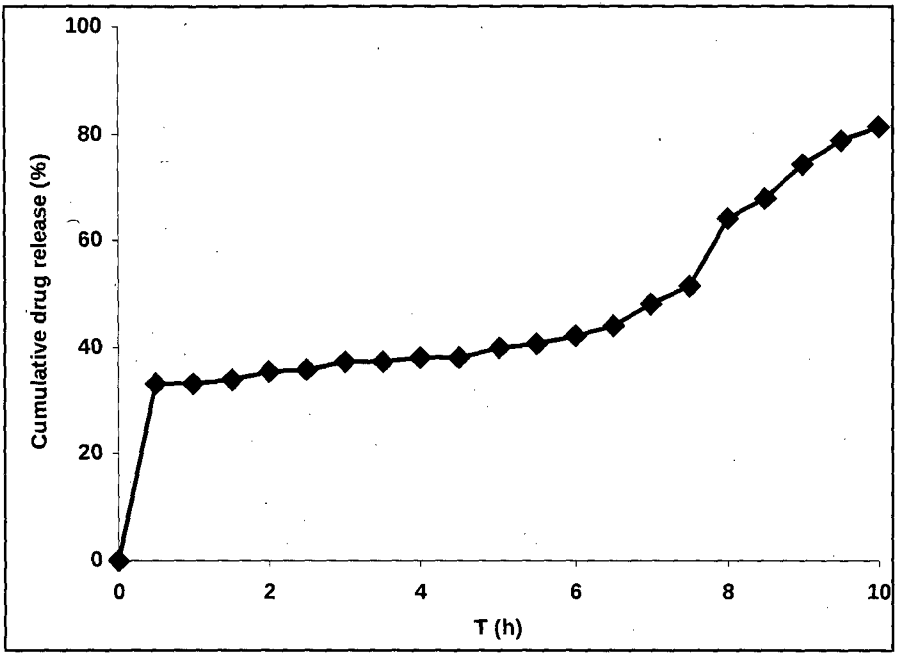


Figure 9

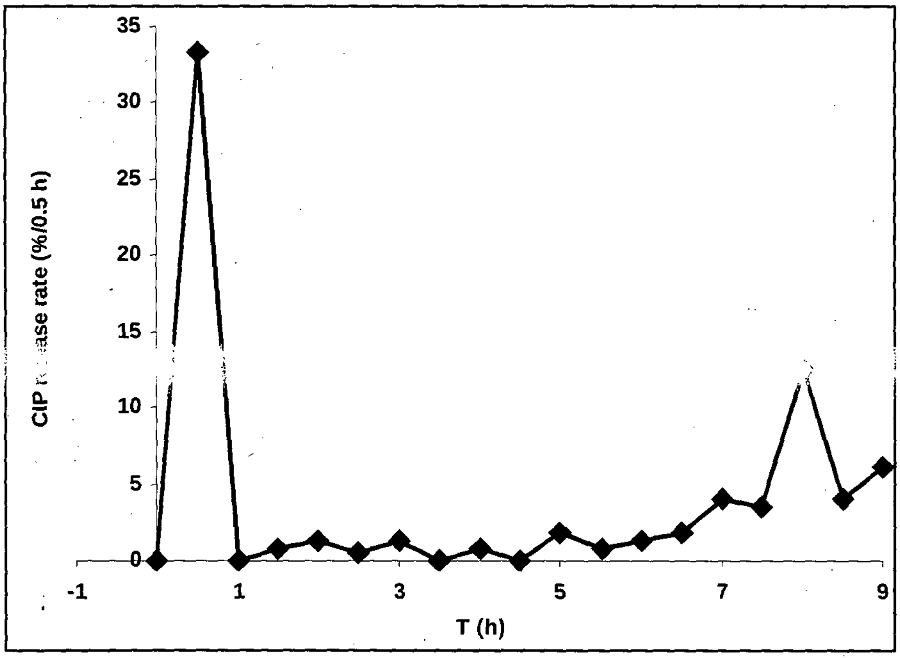
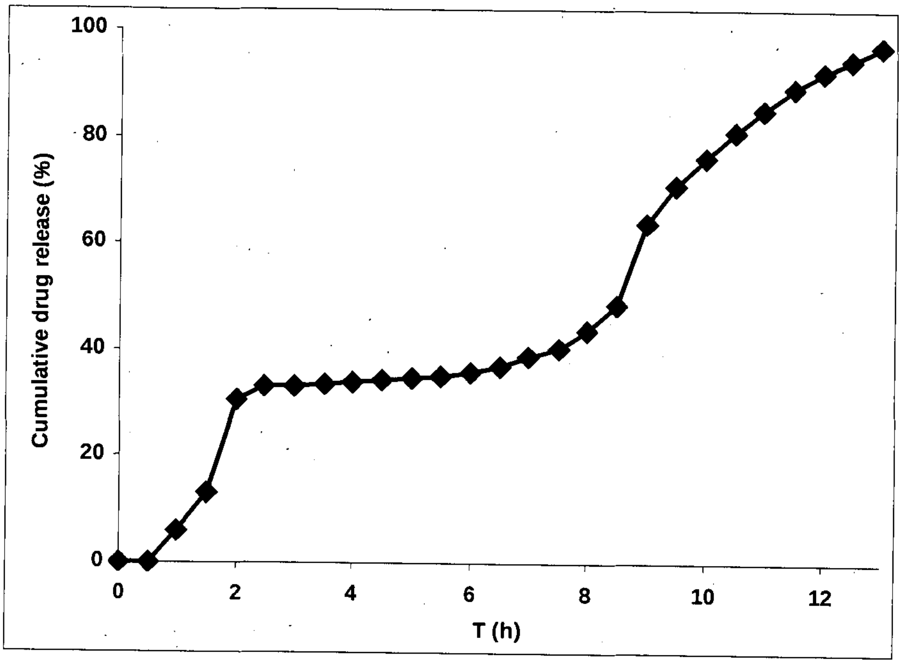


Figure 10



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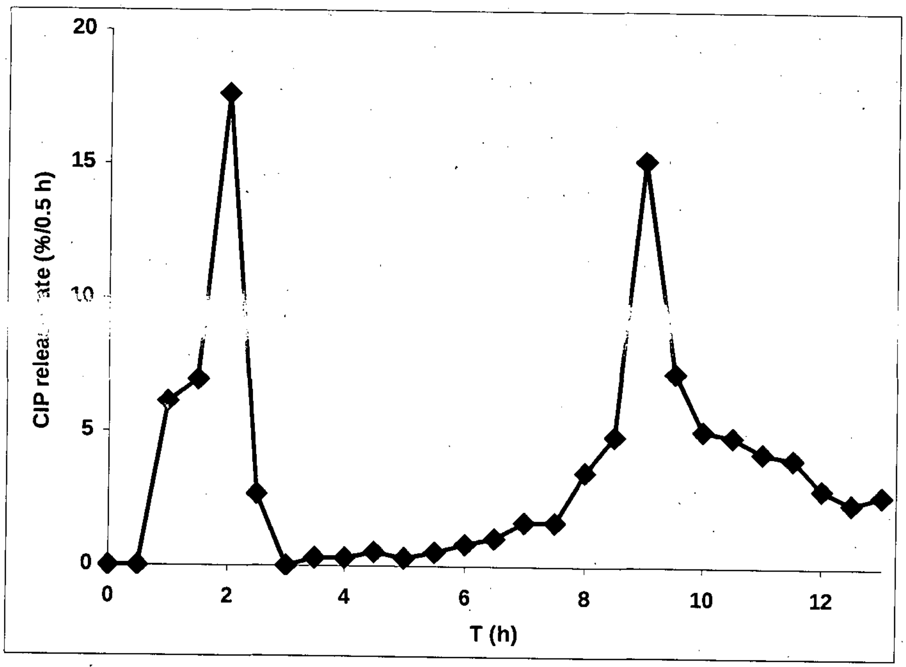


Figure 12

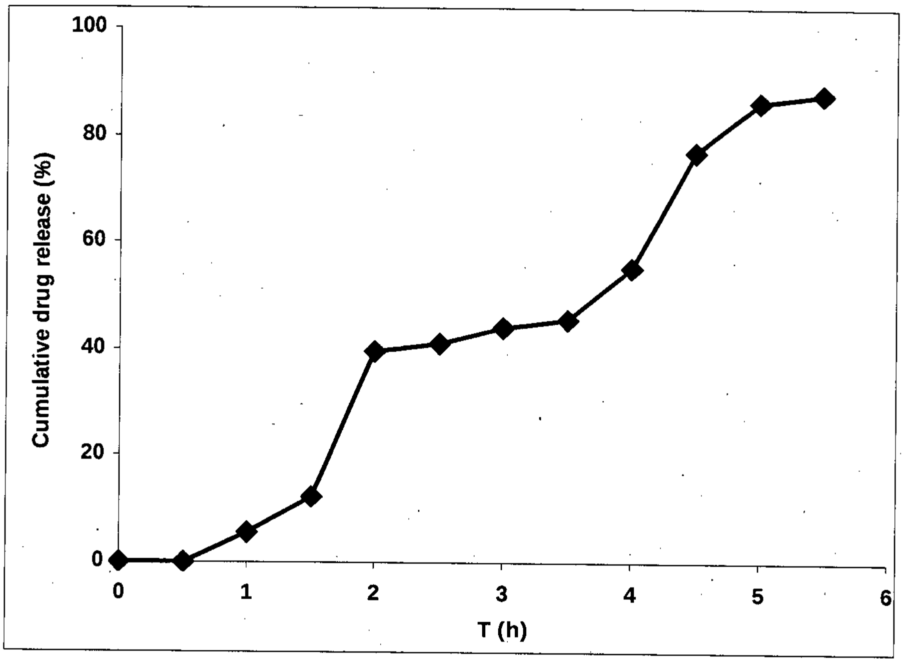


Figure 13

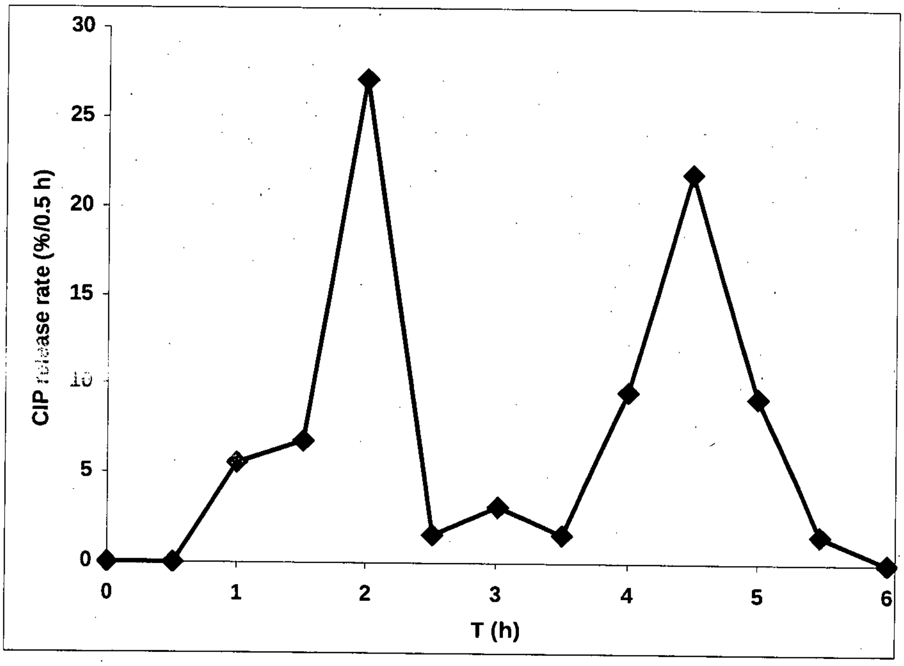
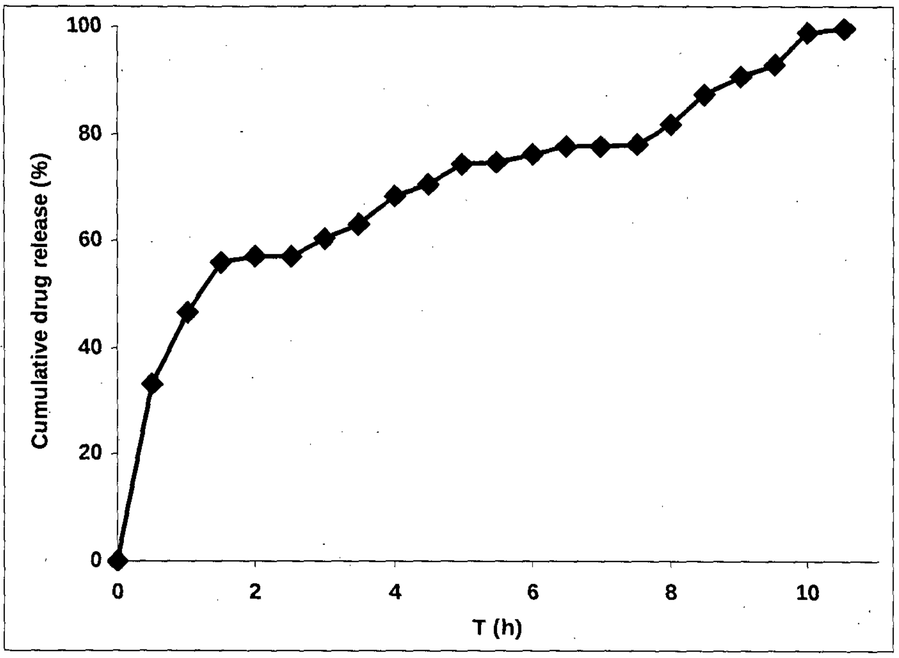


Figure 14



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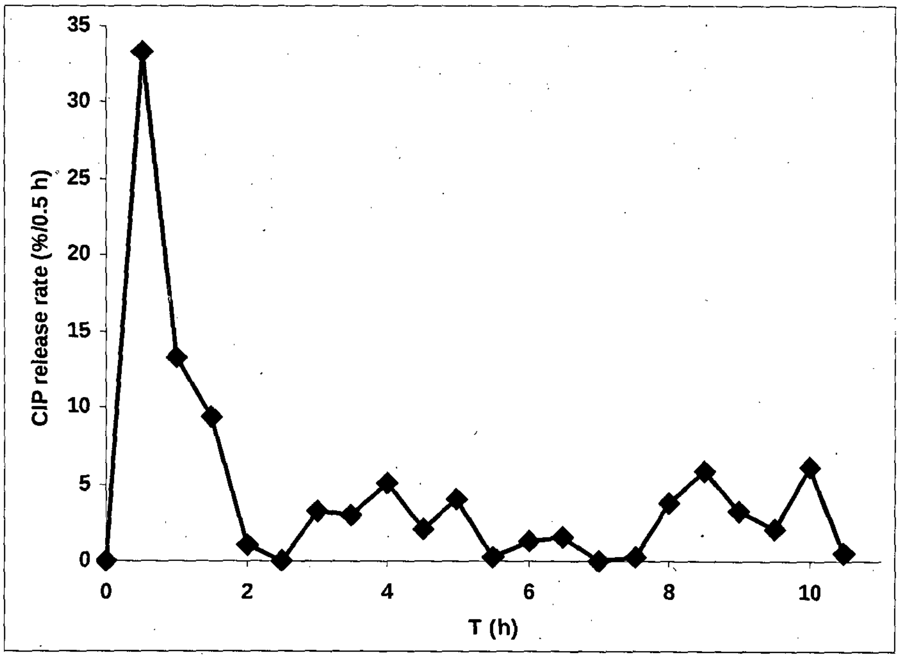

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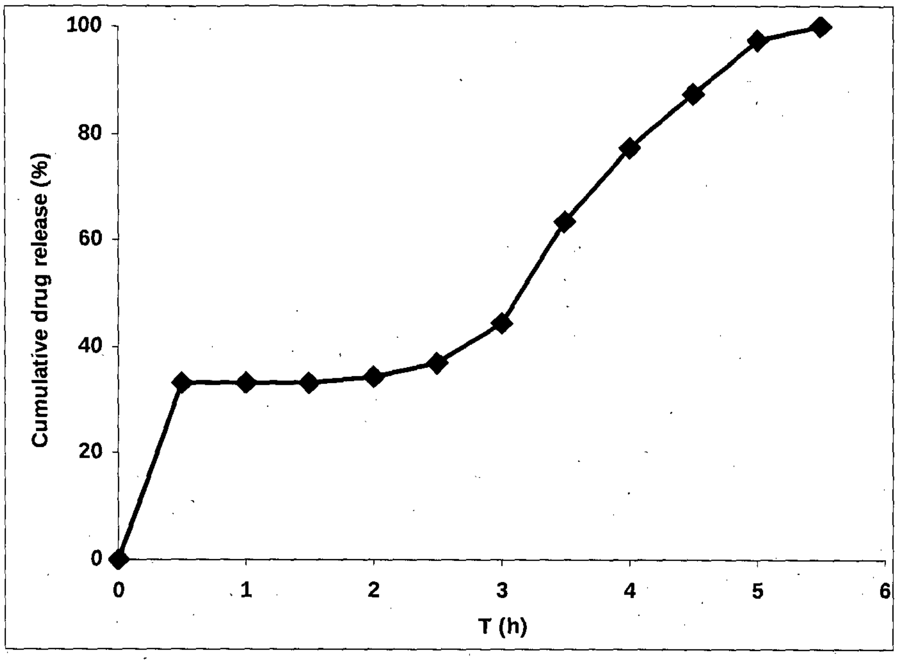

Figure 17

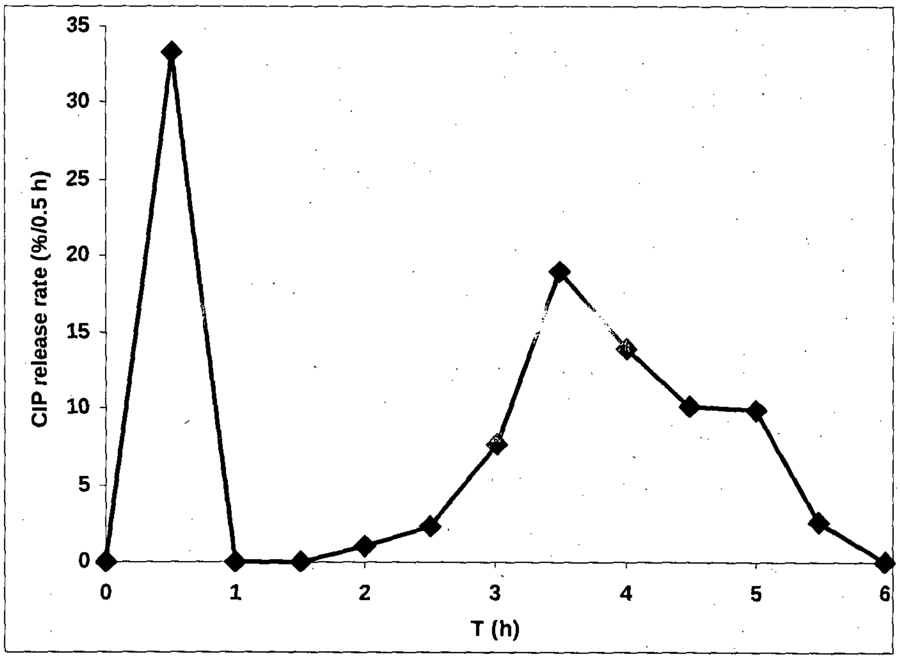

Figure 18

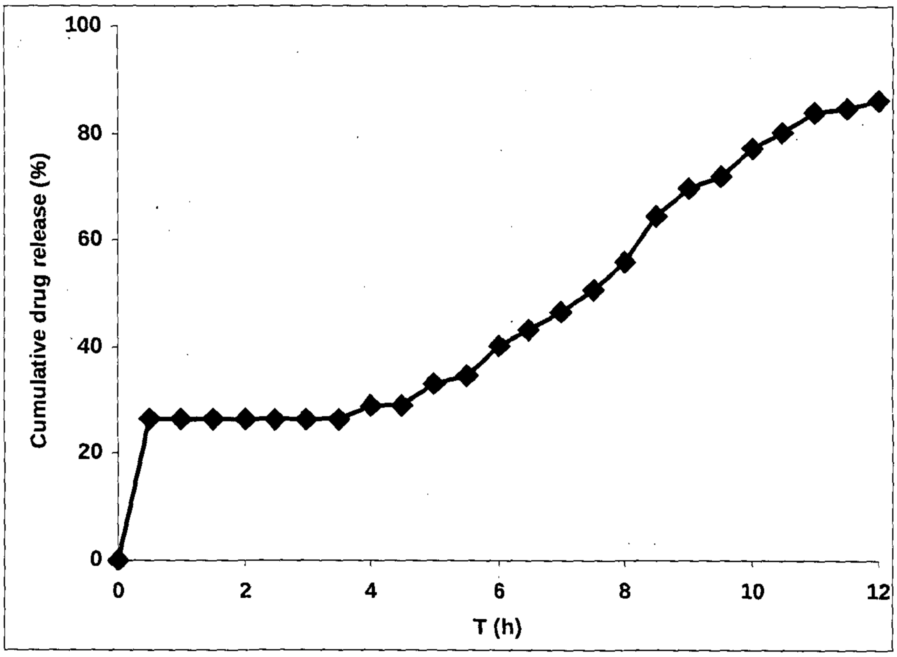

Figure 19

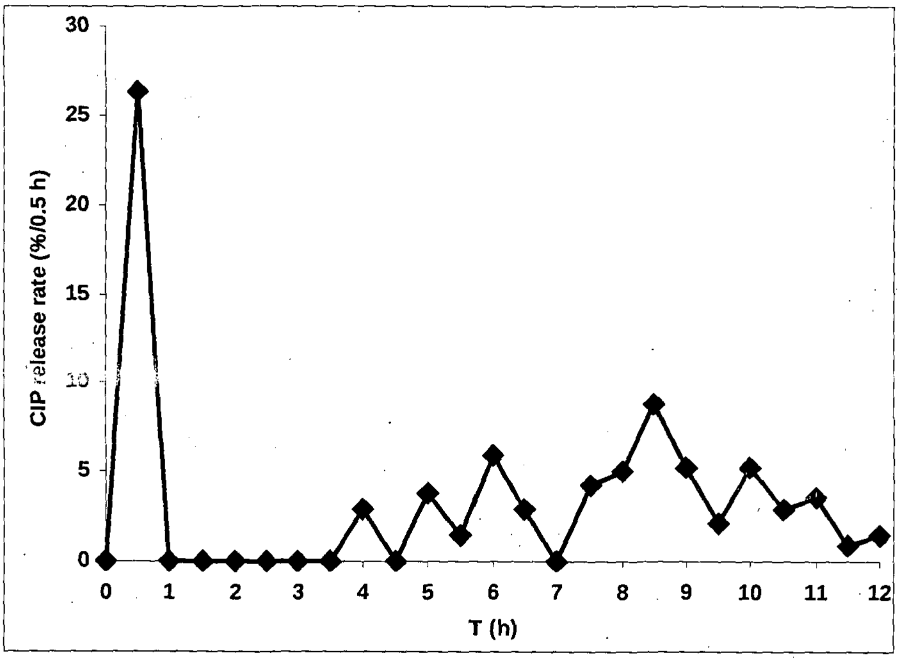

Figure 20

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000662

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/134054 A1 (KULKARNI MOHAN G [IN] ET AL) 22 June 2006 (2006-06-22) cited in the application page 4, paragraphs 39, 40 page 6, paragraph 72 page 8; tables 4, 5 -----	1-19
A	US 2005/281874 A1 (MENJOGE ANUPA R [IN] ET AL) 22 December 2005 (2005-12-22) page 3, paragraph 37 page 4, paragraphs 46, 55 page 5, paragraph 58 -----	1-19
A	WO 2011/111068 A2 (COUNCIL SCIENT IND RES [IN]; MUTHUSAMY RAMESH [IN]; KULKARNI MOHAN GOP) 15 September 2011 (2011-09-15) page 7 -----	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

14 February 2013

Date of mailing of the international search report

20/02/2013

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Authorized officer

Laurent, Antoine

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2012/000662

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2006134054	A1	22-06-2006	NONE		
US 2005281874	A1	22-12-2005	NONE		
WO 2011111068	A2	15-09-2011	EP 2544666	A2	16-01-2013
			US 2013004434	A1	03-01-2013
			WO 2011111068	A2	15-09-2011