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Optimization and formulations for design of "Lag Phase" in the multilayer drug delivery system of amlodipine besylate and atorvastatin calcium

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ABSTRACT

Multilayer biodegradable polymer drug delivery, time dependent release has many exceptional advantages in controlled drug delivery system. The inception of layer by layer constructed tablet-in-capsule facilitated release of drug in accordance of stimuli response carrier system. Atorvastatin calcium and Amlodipine besylate were chosen a model drug because of its poor absorption in gastrointestinal tract. Three layer multiple unit consist of 10mg Amlodipine besylate blend, lag phase and 20 mg Atorvastatin calcium blend that was compressed into tablet plug and snuggly fitted into the impermeable hard gelatin capsule body and closed by soluble cap of capsule shell. Both the layers of drugs act as a immediate release tablet at the time of delivery were compared and evaluated with market formulation of caduet tablets with strength of 10g Amlodipine Besylate and 20mg Atorvastatin calcium. 3^2 full factorial design was used to study the effect of two variables. The proportions of hydrophillic polymers like chitosan and sodium starch glycolate had the most significant effect on the release of drug. A zero order of polynomial equation was fitted to data and resulting equation is used to predict the response in optimal region.

Keywords: lag phase, three layer drug delivery system, Multilayer drug delivery, Swelling layer, Pulsatile drug delivery

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INTRODUCTION

Cardiovascular disease (CVD) is leading cause of death and disability and associated with high cost of health care. In CVD, hypertension and dyslipidemia are highly prevalent because they act synergistically. Although treatment of hypertension and dyslipidemia is well established in guidelines but the current risk factors provide poor control over it. A proprietary single tablet, fixed dose combination (caduet 10/20mg) of Amlodipine besylate (dihyrropridine calcium channel blocker) and Atorvastatin calcium (3-hydroxy-3methyl-glutaryl coenzyme A reductase inhibitor, or statin) was established. It is a first kind of combination that designed to target two major cardiovascular risk factors simultaneously. Fixed single dose combination therapy experienced dose related and statistically significant reduction in systolic and low density lipoprotein. There is limitation of these combinations like cost, loss of flexibility, unclear cause of adverse reaction. [7]

With the advancement in the field of chronobiology i.e. ability to deliver the therapeutic agent to patient in staggered profile because circadian rhythm requires the availability of precise technology (Pulsatile drug delivery system). PDDS consists a system where drug is released suddenly after well defined lag time or time gap according to circadian rhythm of disease state. No drug released from the device with this lag time or it would be less than 10 %. [2]

Elevated rate of Cholesterol synthesis take place at night time than day light irrespective of fasting and fed condition. Hence evening dose is more effective in combating the activity of rate limiting enzyme HMG-coA. Blood pressure shows wide variation in early morning. It reaches its maximum at 6 A.M. then gradual declination in the whole day. Hence early evening and early morning single dosing is required for the effective control of hepatic cholesterogenesis and BP soaring. Therefore chronomodulated drug delivery of both the drugs in two pulse system with predefined lag time of 6 h. So that desired pharmacological effect can be achieved. [3, 8]

In the present research paper the kinetic and dynamics of medication are so designed in accordance with biological rhythms like period, level, amplitude and phase. A single tablet-in-capsule dosage form combining Amlodipine besylate, lag phase and Atorvastatin calcium has been developed, which releases the drugs in accordance with biological rhythm of the body. The combination drug therapy for the treatment of CVD associated disease with three layered tablet-in-capsule-dosage form will offer better an effective treatment of disease.

MATERIALS AND METHODS

Chitosan, Sodium starch glycolate, Sodium alginate, Talc, Tragacanth, Gaur gum, Starch (S.D. fine chemicals ltd. Mumbai, India), Magnesium stearate (Merk specialties pvt. ltd. Mumbai India), Lactose (Yarrow chem. products, Mumbai, India), Atorvastatin calcium (Ranbaxy labs lt., India), Amlodipine Besylate (Pravin laboratories ltd. Gujarat, India). Casted in # 0 size hard gelatin capsule containing bilayered tablet of 350 mg plug of Amlodipine besylate, Lag plug and Atorvastatin calcium. All the reagents were of analytical grade and used without further purification.

Preparation of "Lag Phase" in the multilayer drug delivery system

In the present study biodegradable polymers like Sodium alginate, Tragacanth, Gaur gum, Starch were used for the formulation of the lag phase for the effective drug release in biodegradable multilayer drug delivery system with predefined time. The lag time of lag phase is function of the composition of the outer polymer layer. The Lag time composed Various Hydrophilic Polymers which are listed below in table I. [1]

Casting of the swellable granules

The swellable polymer (100–200mg) was prepared by granulating different hydrophilic polymer like Sodium alginate, Tragacanth, Starch, Gaur gum, with Lactose. These Granules were dried in an oven at 40.C for 12 h then compressed into mini tablet for the further optimization. The dried mini discs were carefully removed and stored in desiccators until further testing. [4]

Swelling Index (% water uptake studies)

Swelling index experiments (n=3) were performed. A predetermined approximate weight of the sample granules were placed over the watch glass (already weighed) onto filter paper. The swelling medium of 0.1N HCL was added up to the level of the watch glass. Watch glasses were covered to avoid water evaporation. As the penetration takes place, the swelling medium was taken up by the sample Granules. This water flux resulted in a weight change of the granules and was weighed with a digital balance as a function of time as shown in graph I (a,b,c,d). The water uptake was calculated as. [5]

% water uptake = wt-wo/wo *100

Where wt is initial wt of disc, wo is final wt of disc

Lag time capsule shaped PDDS

Compressed tablet of lag plug was placed into USP II paddle apparatus rotation speed 50rom was maintained for s period of 10 hr in medium of phosphate buffer 7.4 pH at 37ºC. The lag time was defined as the time point when the outer coating ruptured due to swelling as shown in graph II (a.b.c.d). [4]

Hardness test

The development of compressed tablet in PDDS is promising area in pharmaceutical research, concerned with high control over the release rate of drug combined with flexibility in the adjustment of the both the doses and the release of drugs so the hardness can be optimized for time dependent lag time for Pulsatile drug delivery system. The force

when compressed tablet were broken by Monsanto hardness tester was measured using to assess the lag time as described in graph III (a,b,c,d). [4]

Preparation of Pulsatile Release Amlodipine Besylate Tablet immediate release first pulse (FP1)
The polymers, gave minimum swelling in acidic buffer and maximum swelling in basic media were selected for this study. Sodium starch glycolate was used as natural polymer (superdisintegrant) for the immediate release of Amlodipine Besylate from the Pulsatile system. Microcrystalline cellulose was used as filler, magnesium stearate was used as a lubricant and purified talc as a glidant. These entire ingredients were mixed together in mortar and pestle. A theoretical weight of about 80±2mg powder was fed manually in to die of 10 stations (Rimek minipress-1, Ahmadabad, India) and compressed by using 6 mm flat faced punch by direct compression method. This is used as pulse in multilayered drug delivery system. As given in table II c. [6]

Preparation of Atorvastatin calcium tablet immediate release Second pulse (SP2)
Atorvastatin calcium blend was prepared for second pulse immediate release of drug by direct compression method. Chitosan was used as a natural super disintegrating agent. Starch used as a filler and provide uniform adhesion to another layer without forming capping and lamination defects. MCC used as filler in sufficient quantity. Each formulation was mixed in a mortar pestle. The resultant blends were tableted to 120±2 mg using die of 10 stations (Rimek minipress-1, Ahmadabad, India) and compressed by using 6 mm flat faced punch by direct compression method. As given in table II d. [5]

Formulation of swelling layer for lag phase
A theoretical weight of about 150 mg powder of 50% sodium alginate and 50% of lactose was fed manually into die over the tableted Amlodipine tablet for lag phase of 10 stations (Rimek minipress-1, Ahmadabad, India) and compressed by using 6 mm flat faced punch by direct compression method. This will provide lag phase in multilayered drug delivery system. [6]

Preparation of impermeable capsule body
The impermeable capsule body is constituted of gelatin of 0 # size. Gelatin capsule was treated with formaldehyde for 24 hrs in desiccators. So that it becomes saturated with epoxy ion, make capsule body impermeable. Afterwards, the capsule body and the untreated soluble cap were stored in desiccators for further use. During the experimental time, the gelatin capsule body shows no water permeability and can be used in this study for the daily administration. [6]

Fabricating of capsule device for three pulses drug release with bi-layered tablets served as the third pulse
The three-layered tablet was inserted into the capsule body with a soluble cap. 250 mg lactose was added to assure the upper surface of the tablet flushed with the open end of the capsule body. The tablet (350 mg, diameter 6 mm) fitted snuggly with the wall of the capsule. The bilayered tablet is substituted by lag phase, both the upper and lower layers served as rapid release layers.

Lag time of chronomodulated drug delivery system of Amlodipine besylate and Atorvastatin calcium
The chronomodulated capsule drug delivery systems were placed in the beaker with variable dissolution medium. Lag time describes where drug releases uni-directionally and drug showed less than 10% of actual drug amount. [5]

RESULTS AND DISCUSSION

Modified drug release dosage forms offer definite advantages over conventional release formulation of same drug or different drugs, hydrophilic polymers are mainly used for preparation of matrix type controlled drug delivery system. These systems usually provide non-linear release profile. The multilayered matrix system overcomes inherent disadvantages of non-linearity associated with diffusion controlled matrix devices by providing additional release surface with time to compensate for the decreasing release rate. [1]

The proposed capsule shaped drug delivery system consists of insoluble gelatin capsule insoluble body and two layered drug assembly with a lag plug. The lag plug was optimized on the basis of swelling index, hardness and time dependent release. The lag plug was successfully formulated in three different loads like, 100 mg, 150 mg, and 200mg with four different hydrophilic biodegradable polymers. Depending upon its gelling nature optimum concentration was taken as described in table I. [2]

Swelling index

Swelling index (the water uptake) was determined by standard reported method. The optimum amount of water was taken up with the 150 g punch. The superdisintegrants, Sodium alginate, Gaur gum, Tragacanth and Starch, with lactose as filler or binder can swell more freely under the 150mg load, resulting in a lower mechanical work/energy. In other words, if a heavier load was pushed upwards by the swelling superdisintegrant, it exerted more mechanical work or swelling energy with greater time. The ratio of developed swelling index to the amount of water up taken resulted in appropriate lag time using sodium alginate as depicted in I (a,b,c,d). Higher the water uptake, the higher in the observed swelling energy of the gel-like structure formed under a certain load. [4]

The proposed capsule-shaped Pulsatile DDS consisted of a drugs-containing gelatin capsule 5 mm diameter as the top and bottom layer, a swelling layer or lag phase in between and an external polymeric coating as a capsule. The swelling layer was formed from direct compression of swellable polymer and lactose granules. The swelling behavior of cast discs containing the swelling layer and lactose which simulated the swelling layer of a rupturable Pulsatile DDS. An effect of the type of the swellable polymer was different as per their chemical behavior. The cast sample discs in combination with a binder were compared to characterize their swelling potential. In contrast, sodium alginate and tragacanth developed a detectable swelling index and the punch moved significantly as depicted in graph I. Sodium alginate showed the highest degree of swelling under 150 mg loads and was, therefore, selected for the use in the swelling layer of the Pulsatile DDS and was further investigated. These results were in good agreement with results from other studies conducted further, where sodium alginate had a superior effectiveness as a lag phase when compared with other biopolymer. [5]

A Pulsatile DDS with a more and lesser thicker swelling layer would develop the critical swelling energy, which is necessary to break the outer coating film faster. Therefore, the lag time of the Pulsatile DDS has to be in desired range.

The swelling layer consisted of the swellable polymer, Sodium alginate, and the binder lactose. The Sodium alginate particles would not adhere to the capsule surface without a binder. Lactose was, therefore, responsible for the formation of the swelling layer from the Sodium alginate particles on the hard gelatin capsule shells. Increasing the amount of Sodium alginate and reducing the amount of lactose within the swelling layer increased the lag time and vice versa. The amount of Sodium alginate could not be increased further, because an amount of binder was needed to form the cast discs or the swelling layer, which otherwise became too brittle and could not form a mechanically stable layer. Hence sodium alginate with 50 percent with lactose of 150 mg load is optimized for further use. [5]

Effect of the medium on the swelling behavior of drug release

Since an orally administered DDS comes into contact with gastro-intestinal fluids of different pH and ionic strength, it was also important to investigate the swelling behavior of Sodium alginate, Tragacanth, Gaur gum, and Starch in different media. The release behavior was optimum in purified water and phosphate buffer pH 7.4. The lag time dependent onto release in 0.l N HCl was affected as described in graph II (a,b,c,d). This could be attributed to the presence of carboxylic groups in Sodium alginate. In an acidic environment, the carboxylic groups were unionized, thus resulting in a lower water uptake and swelling. In order to confirm these observations, the swelling samples were also investigated in the simulated rupture test in different media. The lag times corresponded well to swelling energy data. The lag times in purified water and buffer pH 7.4 (USP 25) were optimum and similar. The time to rupture was prolonged in 0.1 N HCl. This can be explained by lowering in swelling behavior and the slower rate of fluid penetration, resulting in a later rupture of the outer polymer coating. [5,6]

A binder was necessary to cast superdisintegrant containing discs, however, the binder could also influence the swelling behavior, either by a spatial separation of the swelling particles or by a competition for free water after the binder was dissolved. Sodium alginate led to 6-7 hrs lag time and a complete rupture of the outer coating in the simulated rupture test. Tragacanth, gaur gum and starch showed a desired coating rupturing, which can be explained by a higher retardation of the water penetration into the swelling layer by Sodium alginate, building a highly viscous gel. [6)

Hardness

It establishes the relation between impacts of tablet on lag time of multiple drug delivery systems. As the whole lag plug will be inserted in the insoluble capsule body. It will provide mechanical strength to the whole Pulsatile drug delivery assembly. However increased hardness may cause high tabletting energy. So prior to the formulation of

multilayered drug delivery system, the hardness of lag plug should between 3-4 kg/cm3 as described in table graph III (a,b,c,d). [5]

Formulation

A 3^2 full factorial design was employed to study the effect of independent variables, i.e. Amount of Sodium starch glycolate (FP1X1) and % of binder as starch (FP1X2) and Amount of Chitosan (SP2X1) and % of binder as starch (SP2X2) for FP2 on dependent variables, i.e. % drug release as described in table II a, II b. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. [3]

$$YFP1 = b0 + b1X1+b2X2 + b12X1X2 + b11X12 + b22X22$$

$$YSP2 = b0 + b1X1+b2X2 + b12X1X2 + b11X12 + b22X22$$

Where, Y is the dependent variables, b0 is the arithmetic mean response of the nine runs, and b1 is the estimated coefficient for the factor X1. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X12 and X22) are included to investigate non-linearity. The results indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F1 to F9) for both the blends. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit. The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates.

Lag time of chronomodulated drug delivery system

Single unit capsule pulsatile drug delivery systems have been developed. The proposed Pulsatile capsule drug delivery system consisted of an insoluble capsule body treated with formaldehyde containing two layers of immediate release drugs, lag phase of lactose and sodium alginate and soluble cap. The addition of binder like lactose was necesary to bind the whole assembles on capsule shell. The polymer eroded slowly within predefined lag time that could be mainly controlled by insoluble capsule body and lag plug. The lag time dependent on polymer concentration and thickness of swelling layer. [3]

The lag time also influenced by nature of capsule weather it is hard gelatin or soft gelatin. The lag time was much longer in hard gelatin in comparison to soft gelatin capsule even at the same coating and composition level. The shorter lag time of soft gelatin capsule depends on degree of fillings with liquid, the pressure developed by the swelling layer is therefore directed primarily towards the outer polymer layer but in hard gelatin capsule degree of fillings is lesser and possess air inside the capsule. The pressure of swelling layer is therefore directed towards the capsule core not towards the outer coating. Hence hard gelatin capsule showed more water retention capacity resulting in the longer lag time at the same coating and composition level. [7]

Based on the data obtained from release profile of Amlodipine besylate and Atorvastatin calcium from FP1 and SP2 batches, Factorial design was applied to formulate the optimum batch. All the batches showed lag time of 5 to 6 hrs. The results shown there is additive effect of filler cum binder like lactose on lag phase. At the initial stage, soluble capsule cap releases due to water solubility of hard gelatin capsule but capsule body showed no water absorption because epoxy bond formed during saturation of capsule body with formaldehyde. Initially dissolution media was 0.1 N HCL Amlodipine besylate drug is water soluble drugs, The batches showed rapid release profile due to the burst release of direct compressed plug of drug containing natural superdisintegrants sodium starch glycolate (3-5%). Here drug releases was faster than the required release at their chronological time. Formulation F1 to F3 showed 76.123%, 83.012%, 91.026% respectively and releases drug for longer time, more than three hrs (shorten the window of lag time). Formulation F4, F5 showed 97.012%, 96.079% respectively with shorter lag time (Drug release nearby 10 %), due maximum concentration of sodium starch glycolate (4.8%) and starch (1.8 %). Formulation F7, F8, F9 showed 75.12%, 83.095%, 81.05% respectively due to higher concentration of starch as a binder that restrict the release of drug from the plug as shown in fig IV. Formulation F6 showed 97.03 % optimum rapid release Amlodipine besylate as first release within 2 hrs compare to other formulations and exactly fit in the criteria for drug release. After that dissolution medium was changed into the Phosphate buffer 5.5pH to mimic the GIT. Drug showed 25- 10% release in whole of the lag phase, where insoluble capsule body showed third pulse because lactose filler in the presence of fluid medium with capsule formed impermeable layer, hence unidirectional

passage to the fluid medium. Dissolution was taken in phosphate buffer of 7.4, Atorvastatin calcium showed rapid release with natural superdisintegrant like chitosan (3-6%). Formulation F1, F2, F3 showed respectively 81.23%, 88.02% and 89.08% release with chitosan and starch as polymer here starch concentration is much lower and release was rapid. Formulation F7, F8, F9 showed 74.21%, 78.01%, and 81.02% respectively due higher concentration of starch with chitosan. Starch bind the drug with polymer and slower the rate of release of drug. Formulation F4, F5, F6 showed 74.11%, 78.05%, and 81.32 % respectively showed good release profile compare to other formulation and fit the criteria for the rapid drug release as shown in fig 4. Hence Formulation F6 containing 10 mg Amlodipine besylate, sodium starch glycolate (3.2mg), starch (1.6) as FP1 and Atorvastatin calcium, chitosan (3.6mg), starch (2.4mg) as SP2 with lag plug of lactose and sodium alginate (50:50%) was considered as the optimum formulation according to in vitro dissolution study. [3,7,8]

Table I: Composition of different lag phases of different polymers

Polymers	Filler	Quantity of polymers	Wt of total lag phase (mg)
Sodium alginate	Lactose	10-80%	100, 150, 200
Tragacanth	Lactose	10-25%	100, 150, 200
Starch	Lactose	10-25%	100, 150, 200
Gaur gum	Lactose	15-30%	100, 150, 200

Table II a: Variables in 3^2 full factorial design batches for (first pulse) FP1

Coded values	**Actual Value (%)**	
	X1	**X2**
	Amount of sodium starch glycolate (mg)	**Amount of starch (mg)**
+1	4.8	0.8
1	4.0	1.6
-1	3.2	2.4

Table II (b) : Variables in 3^2 full factorial design batches for (Second Pulse) SP2

Coded values	**Actual Value (%)**	
	X1	**X2**
	Amount of chitosan (mg)	**Starch (mg)**
+1	6.0	1.2
1	4.8	2.4
-1	3.6	3.6

Table II (c) : Design of experiment using 3^2 using full factorial design FP1

	Coded Values		Polymers	
Formulation code	X1	X2	Sodium starch glycolate (%)	Starch (%)
F1	+1	+1	6	1
F2	1	+1	5	1
F3	-1	+1	4	1
F4	+1	1	6	2
F5	1	1	5	2
F6	-1	1	4	2
F7	+1	-1	6	3
F8	1	-1	5	3
F9	-1	-1	4	3

Table II (d): Design of experiment using 3^2 using full factorial design SP2

	Coded Values		Polymers	
Formulation code	X1	X2	Chitosan (%)	Starch (%)
F1	+1	+1	3	1
F2	1	+1	4	1
F3	-1	+1	5	1
F4	+1	1	3	2
F5	1	1	4	2
F6	-1	1	5	2
F7	+1	-1	3	3
F8	1	-1	4	3
F9	-1	-1	5	3

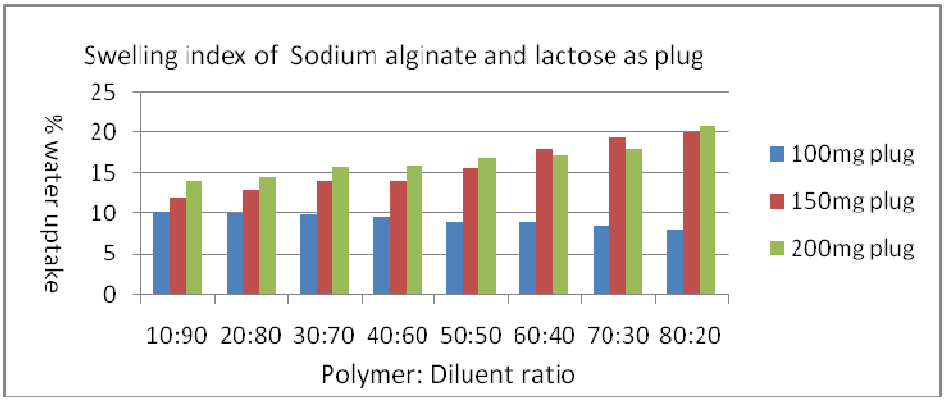
Table III : Formulations of 3^2 full factorial design batches FP1

Formulation Code	Drugs	Variable polymers		lubricant	Glidant
	Amlodipine Besylate	Sodium starch glycolate	Starch (Binder)	Magnesium stearate (%)	Talc (%)
F1	10	4.8	0.8	1	1
F2	10	4.0	0.8	1	1
F3	10	3.2	0.8	1	1
F4	10	4.8	1.6	1	1
F5	10	4.0	1.6	1	1
F6	10	3.2	1.6	1	1
F7	10	4.8	2.4	1	1
F8	10	4.0	2.4	1	1
F9	10	3.2	2.4	1	1

Table IV: Formulations of 3^2 full factorial design batches SP2

Formulation Code	Drugs	Variable polymers		lubricant	Glidant
	Atorvastatin calcium	Chitosan	Starch (Binder)	Magnesium stearate (%)	Talc (%)
F1	20	60	1.2	1	1
F2	20	48	1.2	1	1
F3	20	36	1.2	1	1
F4	20	60	2.4	1	1
F5	20	48	2.4	1	1
F6	20	36	2.4	1	1
F7	20	60	3.6	1	1
F8	20	48	3.6	1	1
F9	20	36	3.6	1	1

a)



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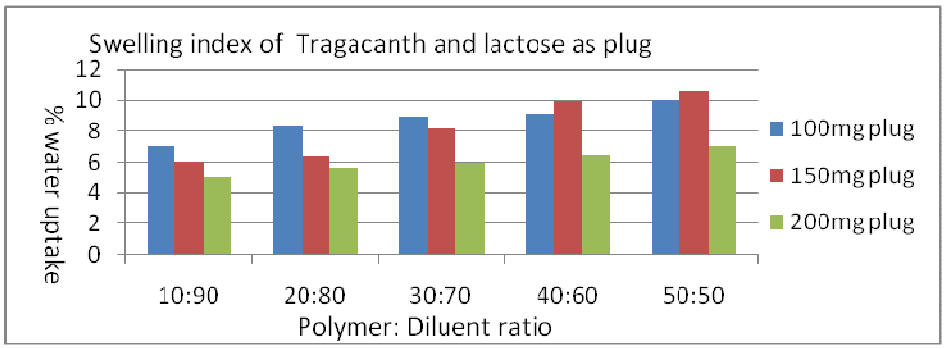

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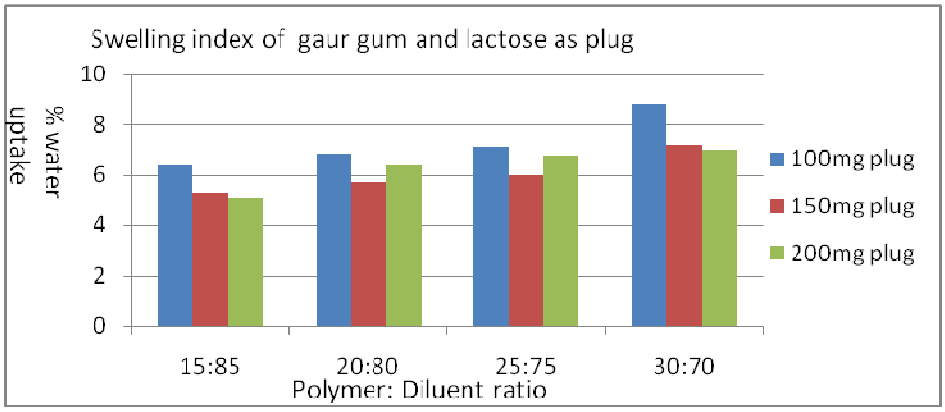

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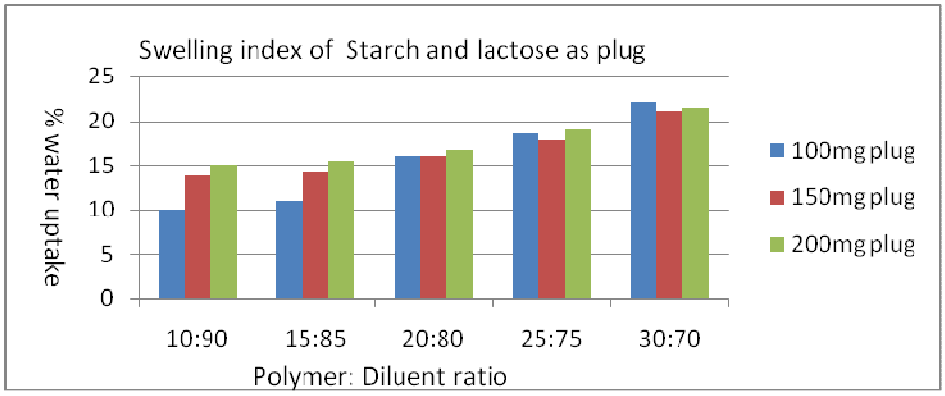
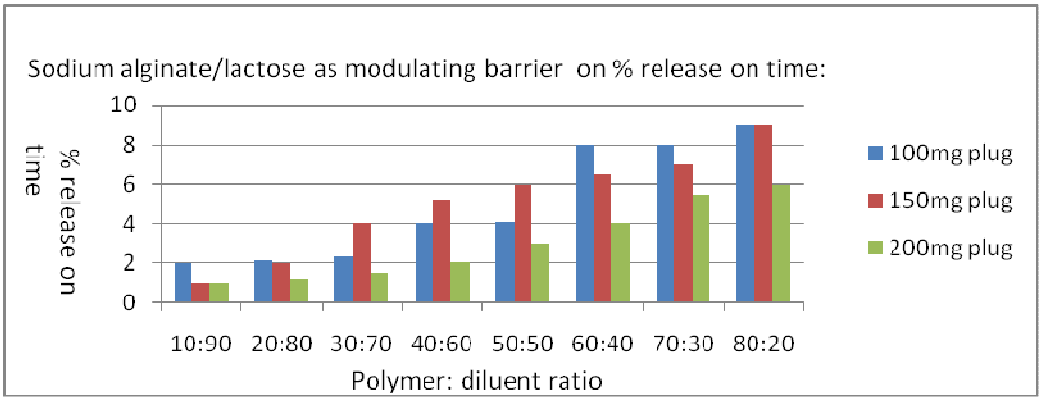
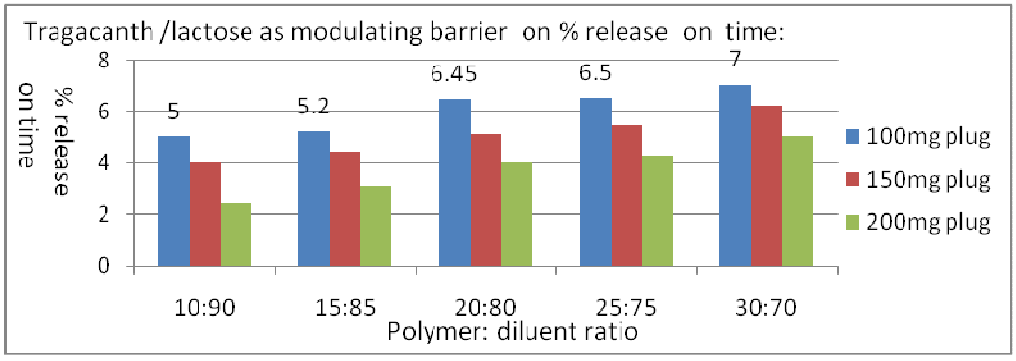


FigI: Swelling index of a) Sodium alginate: lactose, b) Tragacanth: lactose, c) Gaur gum:lactose, d) Starch:lactose





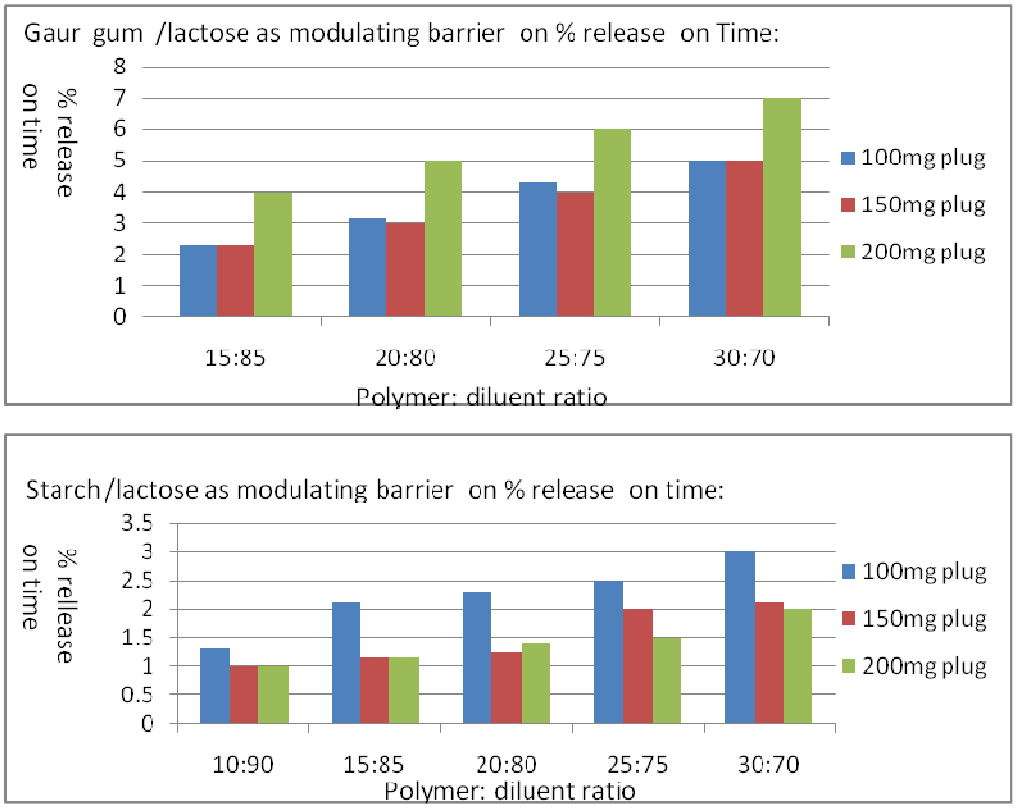
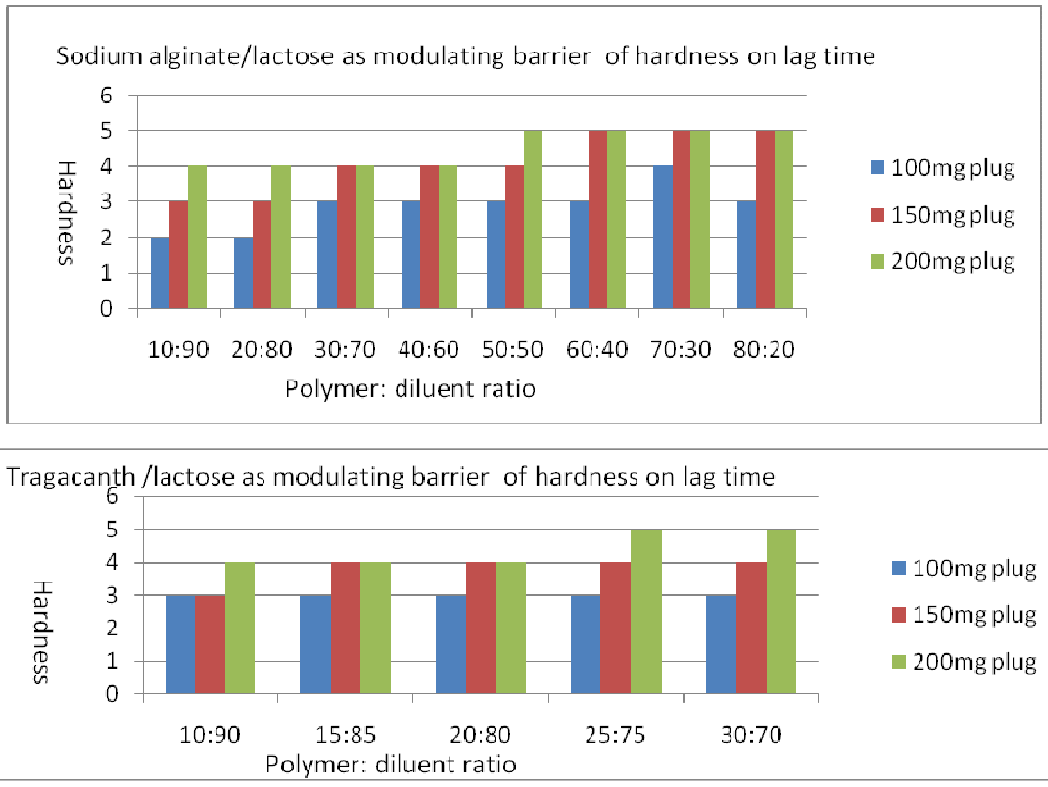


Fig II: Influence of various barrier on % release on time of a) Sodium alginate: lactose, b) Tragacanth: lactose, c) Gaur gum:lactose, d) Starch:lactose



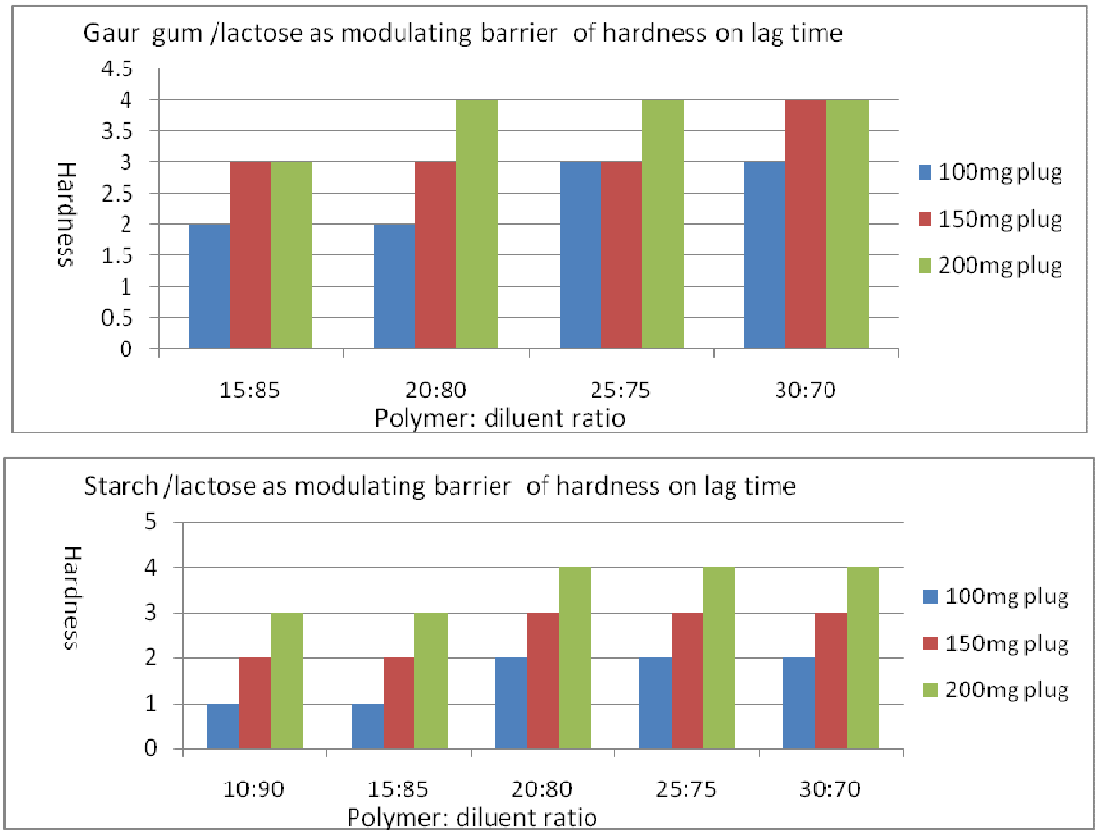


Fig III : Influence of various modulating barrier on hardness on lag time: a) Sodium alginate: lactose, b) Tragacanth: lactose, c) Gaur gum:lactose, d) Starch:lactose

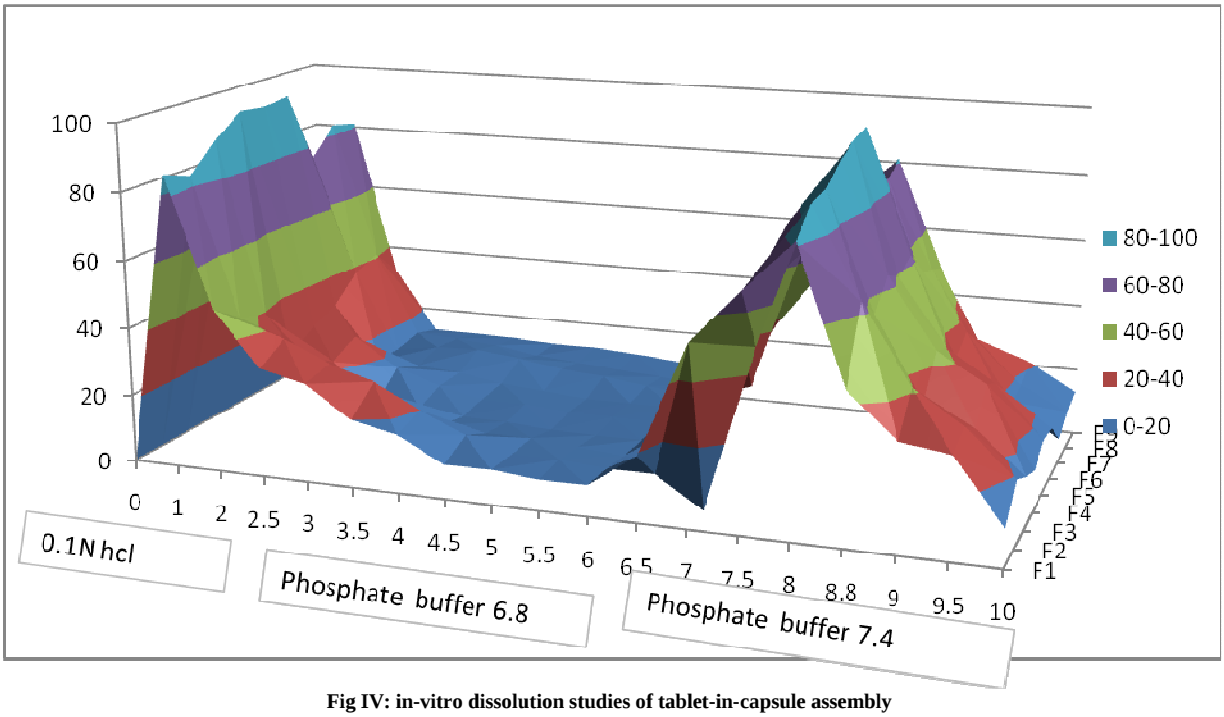


Fig IV: in-vitro dissolution studies of tablet-in-capsule assembly

CONCLUSION

In the present work the suitability of swellable polymer as a swelling layer in capsule shaped Pulsatile drug delivery system was demonstrated. The swelling of lag phase and unidirectional flow of medium characterized as a time dependent process with optimized swelling force with fixed plug. Erodible tablet plug for the capsule assembly formulated using 50% of sodium alginate with 50% of lactose show desired prolongation of lag time. Due to the presence of carboxylic acid in sodium alginate, the swelling was lower in an acidic environment and at higher than the swelling of the other materials tested. Hence water mobility and medium uptake during wet granulation or dissolution would be driving force for the exertion and release of energy. This results in slower plug erosion, and hence an increased lag time from first pulse to second pulse.

The design of two different drug releases at different phases can be adjusted in table-in-capsule designed delivery system, according to the therapeutic needs. The results obtained with dissolution test show that the release profile is dependent on time and Lag plug composition. Formulation F6 containing 10 mg Amlodipine besylate, sodium starch glycolate (3.2mg), starch (1.6) as FP1 and Atorvastatin calcium, chitosan (3.6mg), starch (2.4mg) as SP2 with lag plug of lactose and sodium alginate (50:50%) was considered as the optimum formulation .

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