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DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS FOR PRAVASTATIN

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ABSTRACT

Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. The present work is to develop and evaluation of press coated tablets of pravastatin by using polymers like Ethyl cellulose, carbopol. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that F3 of core tablet and F10 of coated tablet were maintained lag phase upto 6hrs and brust release was at 7th hr and followed by maximum release at the end of 8th hr, so it is selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Pravastatin can be successfully used as a time dependent modified Chronopharmaceutical formulation.

Keywords: Pravastatin, SSG and lycoat and Ethyl cellulose, HPMC K15M.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the arena of pharmaceutical research and development sector [1]. Such systems offer temporal and /or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration [2].

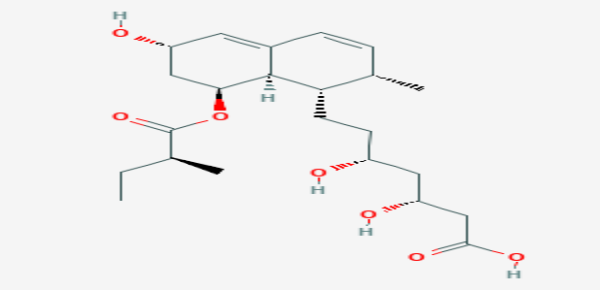
Drug Profile

Pravastatin

Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered [3]. It is a ring-opened dihydroxyacid with a 6'-hydroxyl group that does not require *in vivo* activation. Pravastatin is one of the lower potency statins; however, its increased hydrophilicity is thought to confer advantages such as minimal penetration through lipophilic membranes of peripheral cells, increased selectivity for hepatic tissues, and a reduction in side effects compared with lovastatin and simvastatin [4].

CAS Number: 81093-37-0
Molecular Weight: 424.5277
Molecular Formula: $C_{23}H_{36}O_7$
Appearance: Powder

Structure:



Melting Point: 171.2 - 173°C

Mechanism of action

Pravastatin is structurally similar to the HMG, a substituent of the endogenous substrate of HMG-CoA reductase [5]. Unlike its parent compound, mevastatin, and statins such as lovastatin and simvastatin, pravastatin does not need to be activated *in vivo*. Its hydrolyzed lactone ring mimics the tetrahedral intermediate produced by the reductase allowing the agent to bind with a much greater affinity than its natural substrate.

Excipients Profile

Crospovidone

Synonyms: Cross-linked povidone; Kollidon CL; Polyplasdone XL.

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Chemical Name and CAS Registry Number
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 1–5% concentration in tablets prepared by direct-compression or wet- and dry- granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer.

Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

Croscarmellose Sodium
Synonyms: Ac-Di-Sol; cross-linked carboxymethyl cellulose sodium; *Explocel*.

Chemical Name and CAS Registry Number
Cellulose, carboxymethyl ether, sodium salt, cross-linked [74811-65-7]

Empirical Formula and Molecular Weight

The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.

Hydroxypropyl Methylcellulose
Non proprietary names: B.P: Hypromellose.
Eur Ph: Methylhydroxypropylcellulosim.
USP: Hydroxypropyl methylcellulose.
Synonyms: Cellulose, Hydroxypropylmethyl ether, Methocel, HPMC, Methylcellulose, Propylene glycol ether, Methylhydroxy Cellulose, Pharmacoat.

Chemical Name: Cellulose,2-Hydroxypropylmethylether.

Molecular Weight: 10,000-15,000.

Category: Coating agents, Film formers, Stabilizing agents, Suspending agents, Tablet binder, and Viscosity increasing agent.

Description: HPMC is an odourless tasteless, white or creamy-white coloured, fibrous or granular powder.

Solubility: Soluble in cold water, insoluble in Chloroform, Ethanol and Ether, but soluble in mixtures of Ethanol and Dichloromethane and mixtures of Methanol and Dichloromethane.

Viscosity: The viscosity of polymer ranges from 75-140% of declared value.

Stability: It is a stable material although it is hygroscopic after drying. Increase in temperature reduces the viscosity of solutions. It undergoes a reversible solution to get transformation upon heating and cooling respectively. The powder should be stored in a well closed container in a cool, dry place.

Safety: It is generally regarded as a non-toxic and non-irritant material although excessive consumption may have a laxative effect.

Ethyl Cellulose
Nonproprietary Names
BP: Ethylcellulose
PhEur: Ethylcellulose
USP-NF: Ethylcellulose

Synonyms: Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

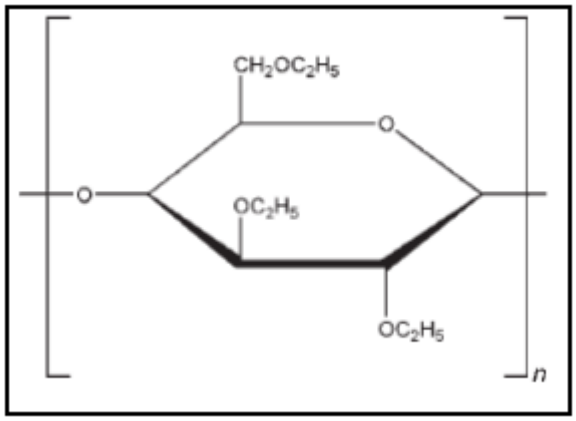
Chemical name and CAS registry number
Cellulose ethyl ether [9004-57-3]

Empirical formula and molecular weight

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of banhydroglucose units joined together by acetal linkages.

Functional category It is used as coating and flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Structural formula



Applications in pharmaceutical formulation or technology

Ethylcellulose is widely used in oral and topical pharmaceutical Formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets andgranules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation.

Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name and CAS Registry Number

Talc [14807-96-6]

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Structural Formula: $Mg_6\ (Si_2O_5)_4(OH)_4$.

Functional Category

Anticaking agent; glidant; tablet and capsule diluents; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent.

Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion. Hardness (Mohs): 1.0–1.5

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds

Magnesium Stearate

Non-proprietary names: Magnesium stearate, Magnesii stearas.

Synonyms: *Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid,* magnesium salt

Chemical Name & CAS Registry number: Octadecanoic acid magnesium salt [557-04-0]

Empirical formula : $C_{36}H_{70}MgO_4$

Structural formula : $[CH_3(CH_2)_{16}COO]_2Mg$

Molecular weight : *591.34*

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Functional category: Tablet and capsule lubricant.

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications: Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Stability and Storage Conditions: Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

Microcrystalline Cellulose

Synonym: Avicel, cellulose gel, crystalline cellulose, E460, mocel, Fobrocel, Vivacel.

Functional category: Tablet and Capsule diluent, suspending agent, Adsorbent, tablet disintegrant.

Applications: As diluents in tablets (wet granulation and direct compression) and capsule formulation. It is also has some lubricant and disintegrant property.

Description: White-colored, tasteless crystalline powder composed of porous particles.

Solubility: Slightly soluble in 5 % sodium hydroxide solution

MATERIALS AND METHODS

Preformulation Studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Determination of Melting Point

Melting point of Pravastatin was determined by capillary method. Fine powder of Pravastatin was filled in glass capillary tube (previously sealed at one end). The capillary tube was tied to thermo meter and the thermometer was placed in the Thais tube and this tube was placed on fire. The powder at what temperature it melted was noticed.

Solubility

Solubility of Pravastatin was determined in pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Pravastatin in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 239 nm [6].

Preparation of Standard Calibration Curve of Pravastatin in 0.1 N HCL

10mg of Pravastatin was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 0.1 N HCL buffer to get 5 to 30µg/ml of Pravastatin. The absorbance of the solution were measured against 0.1 N HCL buffer as blank at 239nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of Standard Calibration Curve of Pravastatin in 6.8 pH buffer

10mg of Pravastatin was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 phosphate buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8 phosphate buffer to get 5 to 30µg/ml of Pravastatin. The absorbance of the solution were measured against 6.8 phosphate buffer as blank at 239nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer [7], Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded

Evaluation of Preformulation parameters

i. Angle of repose.

The angle of repose [8] of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where,

h and r are the height and radius of the powder cone respectively.

Determination of Bulk Density and Tapped Density

5 g of the granules (W) from each formula were introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae [9].

$$\text{Bulk density} = W / V_O$$

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the granules, V_O = initial volume of the granules, V_F = fi Pravastatin volume of the granules.

iii. Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density [10].

Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property [11].

$$C_I = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100$$

Formulation of Compressed Tablets of Pravastatin

The methodology adopted includes:

1) Preparation of core tablets of Pravastatin.
2) Coating of the core tablets

Formulation of core tablets of Pravastatin

The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of Pravastatin, MCC, Crospovidone, Croscarmellosesodium, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Formulation of Coating of the core tablets of Pravastatin

The optimized core tablets were coated with coating ingredients like carbopol and ethylcellulose. Now accurately weighed amount of barrier layer material was transferred into a 10mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets was done in rotary compression tablet machine using 10mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Evaluation of Tablet Properties

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

1. Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average [12]. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented.

2. Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded [13].

3. Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients [14].

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage of friability of the tablets of a badge can be find by the following

Formula:

Percentage Friability = $W1 - W2/W1 \times 100$

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

4. Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

5. Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 40 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The un dissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 239 nm. The concentration of the drug was computed from the standard curve of the Pravastatin in 6.8 phosphate buffer.

6. Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out

in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing 6.8 phosphate buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted [15].

7. *In vitro* Dissolution time

In-vitro dissolution study of core and coated tablets of Pravastatin was carried out using Lab India DS8000 USP dissolution test apparatus. The details are given as below:

Procedure

Tablet was introduced into the basket of the Lab India DS-8000 USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn for half a n hour at 5 min intervals. Samples withdrawn were a analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Evaluation of Pulsatile Drug Delivery Systems

1. Characteristics of Press coated tablets of Pravastatin

Characteristics of tablets of Pravastatin such as hardness and disintegration test were conducted. 3 tablets were taken and hardness of formulations was determined by using Monsanto hardness tester. Average of three determinations was noted down. 6 tablets were taken in Electrolab USP Disintegration test apparatus and disintegration time of tablets was determined using pH 6.8 buffer.

Thickness of coated Pravastatin tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation.

A successful Pulsatile drug delivery system is one that remains intact in the physiological environment of stomach and small intestine for up to six hours, releasing no or minimum amount of drug, but completely releases the drug after six hours.

2. *In-vitro* Dissolution methods

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the pulsatile delivery system might encounter *in-vivo.* The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in 0.1N HCL for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer (PG Instruments T60) for the presence of the drug. Dissolution tests were performed in triplicate.

Despite the simplicity and convenience, conventional dissolution testing primarily provides essential information on the processing specifications of a Pulsatile drug delivery system rather than on the validity of the system design.

Release Kinetic Models

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release.

To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyers-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

Table 1. Formulation Table Of Pravastatin Core Tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Pravastatin	40	40	40	40	40	40
Croscarmellose sodium	2	4	6	--	--	--
Crospovidone	--	--	--	2	4	6
MCC	52	50	48	52	50	48
Mg.stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total wt(mg)	100	100	100	100	100	100

Table 2. Composition of compression coated tablets of Pravastatin

Formulation	F7	F8	F9	F10	F11
Core	100	100	100	100	100
Carbopol	200	-	100	150	50
Ethyl cellulose	-	200	100	50	150
Total weight	300	300	300	300	300

RESULTS AND DISCUSSION

Table 3. Data for Solubility Curve for Pravastatin

S.No	Buffers	Solubility (mg/ml)
1	0.1N HCL	0.125
2	6.8 buffer	0.268
3	7.4 buffer	0.201
4	Methanol	0.869
5	Ethanol	0.751

Table 4. Standard Calibration Curve of Pravastatin at 239 nm

Concentration (µg/ml)	Absorbance
0	0
5	0.121
10	0.239
15	0.372
20	0.514
25	0.637
30	0.776

Table 5. Micromeretic properties of core tablet of Pravastatin

Formulation Code	Derived properties		Flow properties		
	Bulkdensity (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.526±0.26	0.598±0.06	26.26±0.02	12.04±0.03	1.14±0.95
F2	0.516±0.41	0.584±0.01	28.21±0.63	11.64±0.26	1.13±0.74
F3	0.482±0.52	0.567±0.23	25.26±0.46	14.99±0.14	1.18±0.25
F4	0.526±0.85	0.593±0.74	28.63±0.41	11.30±0.85	1.13±0.16
F5	0.509±0.41	0.601±0.45	30.14±0.52	15.31±0.36	1.18±0.05
F6	0.498±0.66	0.562±0.26	27.52±0.26	11.39±0.10	1.13±0.03

Table 6. Post compression parameters of core tablet

	Post compression parameters of core tablet					
	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)	Friability (%)	Disintegration time(secs)
F1	98.12±0.31	3.01±0.10	2.15±0.75	89.63±0.15	0.15±0.09	72±0.196
F2	99.26±0.55	3.26±0.02	3.53±0.42	96.75±0.42	0.52±0.74	59±1.05
F3	97.94±0.24	3.37±0.61	2.14±0.04	98.35±0.35	0.46±0.63	35±0.42
F4	96.42±0.56	3.18±0.16	3.85±0.36	92.28±0.75	0.35±0.28	52±0.63
F5	99.66±0.88	3.56±0.55	2.63±0.42	90.14±0.69	0.18±0.15	46±0.18
F6	97.14±0.19	3.29±0.24	3.05±0.15	97.15±0.04	0.75±0.46	29±0.76

Table 7. Evaluation of Physical Parameters of compressed tablets of Pravastatin

Formula	Weight variation (mean ± SD, mg)	Hardness	Friability (%)	Thickness	Drug content
P1	398.26±1.02	6.05±0.15	0.84±0.26	4.65±0.02	84.15±0.15

P2	397.41±0.26	6.56±0.36	0.75±1.14	4.86±0.21	94.63±0.52
P3	399.52±1.25	7.06±0.48	0.26±0.25	4.92±0.14	91.52±0.63
P4	396.36±0.63	6.45±0.15	0.45±0.26	4.26±0.85	92.15±0.01
P5	397.84±0.74	6.85±0.22	0.31±0.36	4.64±0.39	96.02±0.15

Table 8. Cumulative percent drug release of Pravastatin core tablets of different formulations (F1 to F6)

Time(mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	42.94	53.64	60.53	27.63	40.61	46.37
10	59.34	65.24	73.61	36.94	54.63	55.64
15	66.37	82.63	87.16	40.29	62.93	63.59
20	72.69	89.51	97.36	56.32	76.24	70.49
25	79.34	96.34		62.79	89.35	82.69
30	89.63			73.56	90.36	99.75

Table 9. Cumulative % drug release of coated different formulation (P1F6 to F10)

Time(hrs)	F7	F8	F9	F10	F11
0	0	0	0	0	0
1	12.64	26.35	2.69	2.39	3.62
2	29.65	39.06	3.65	4.61	4.29
3	35.64	46.31	7.94	4.97	5.51
4	49.61	49.75	16.59	5.36	6.29
5	56.75	59.73	27.09	5.97	10.75
6	69.34	67.48	39.67	6.92	13.95
7	77.05	75.22	62.94	89.15	82.64
8	86.95	82.965	76.25	97.34	95.63
9	90.64	93.65	97.64		
10	97.25	99.53			

Table 10. *In-vitro* drug release mechanism of best formulation

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	n
F10	0.578	0.537	0.392	0.680	1.588

Fig: 1. Solubility studies of Pravastatin

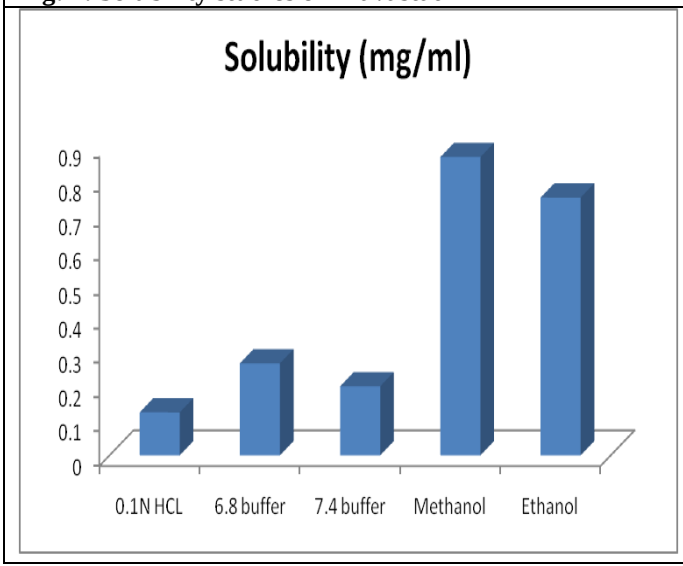


Fig: 2. UV Spectrum of Pravastatin

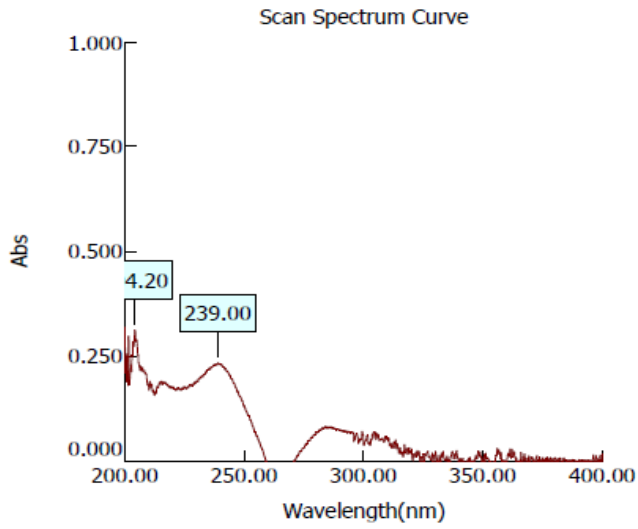


Fig: 3. Calibration curve of pravastatin in 6.8pH buffer

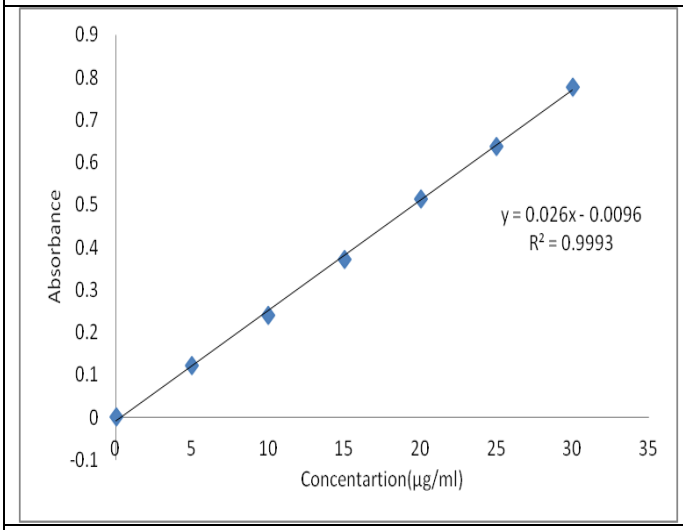


Fig: 4. Cumulative percentage drug release of Pravastatin core tablets F1 – F6

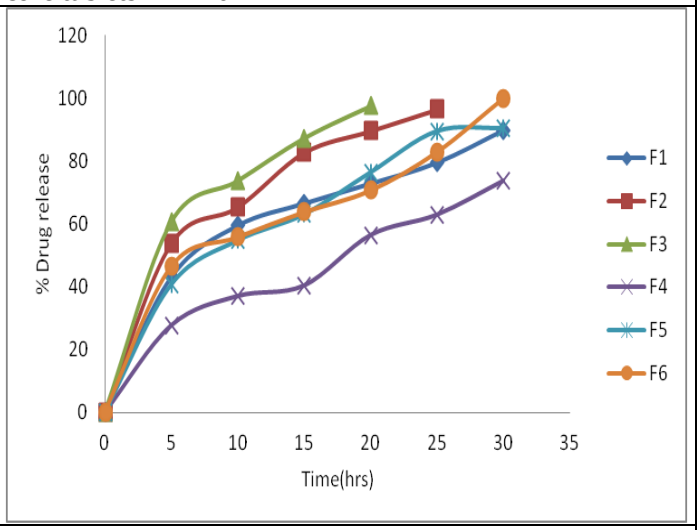


Fig: 5. Cumulative percentage drug release of Pravastatin core tablets F1 – F3

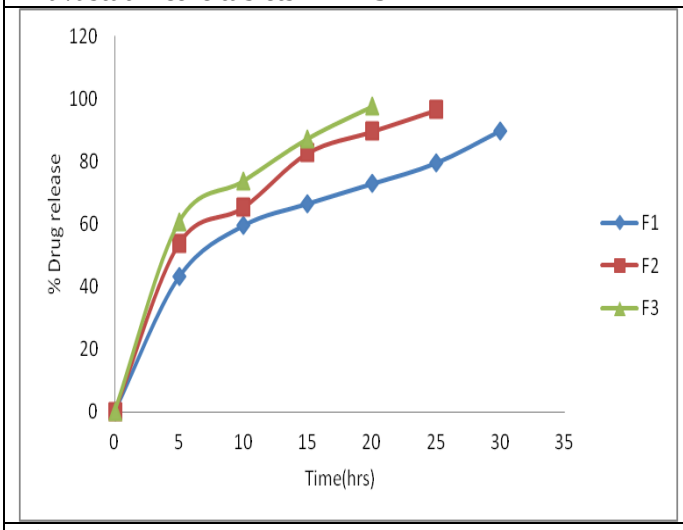


Fig: 6. Cumulative percentage drug release of Pravastatin core tablets F4-F6

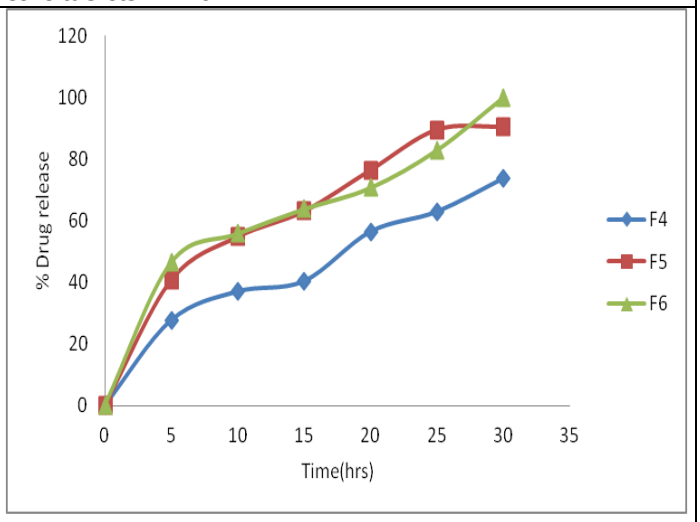


Fig: 7. Cumulative percentage drug release of Pravastatin press coated tablets F7-F11

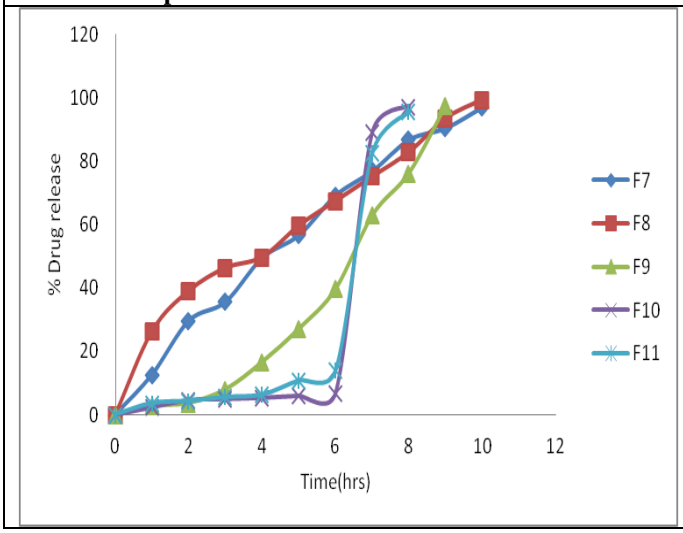


Fig: 8. Zero order release kinetics for best formulation (F10)

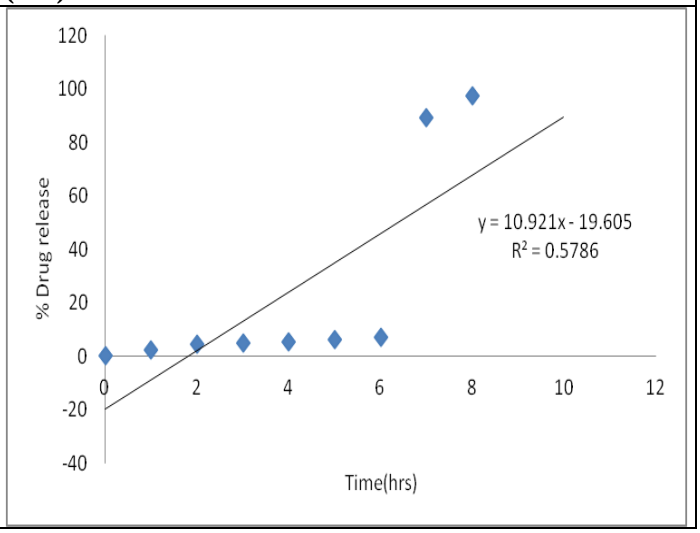


Fig: 9. First order release kinetics for best formulation (F10)

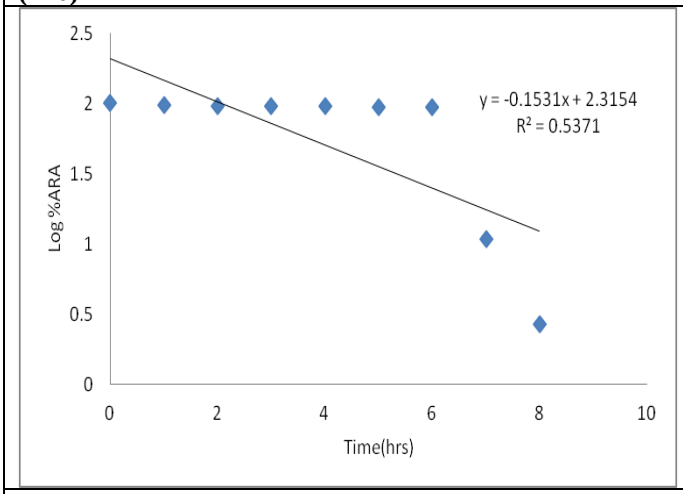


Fig: 10. Higuchi release kinetics for best formulation (F10)

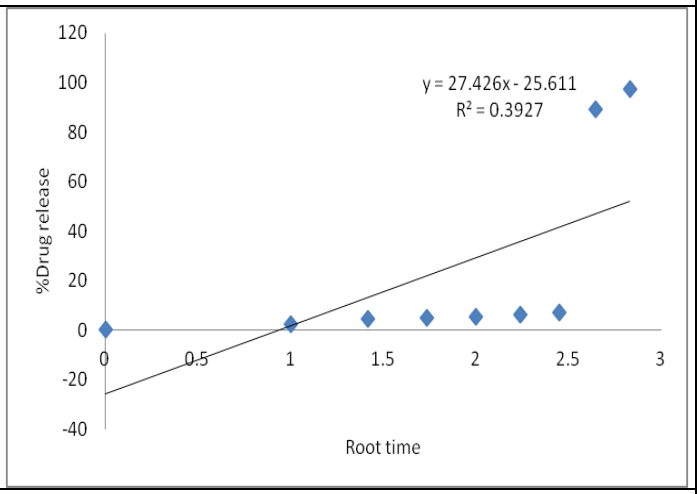


Fig: 11. Peppas release kinetics for best formulation (F10)

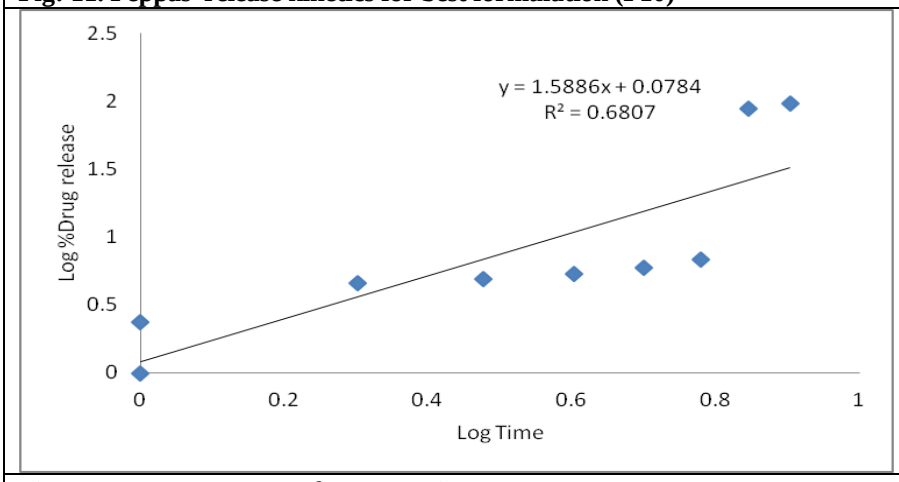


Fig: 12. FTIR Spectrum of Pravastatin pure

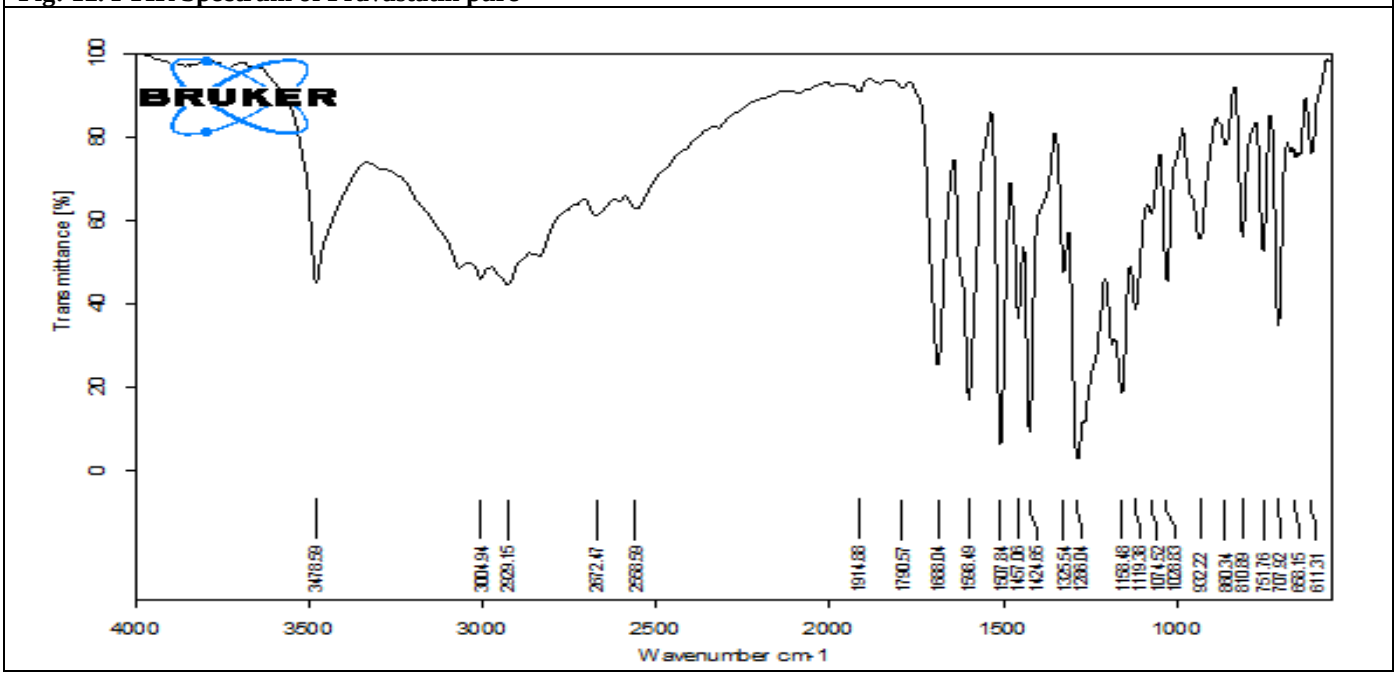
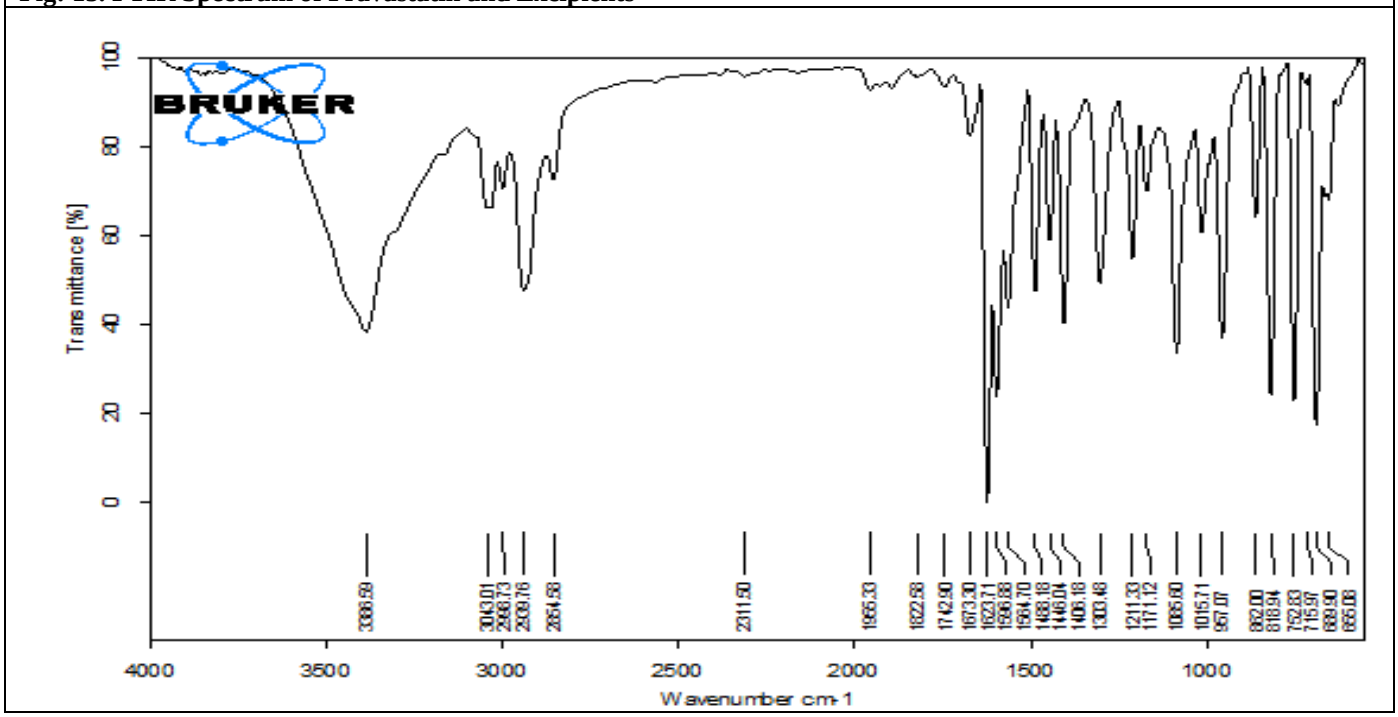


Fig: 13. FTIR Spectrum of Pravastatin and Excipients



Preformulation studies

Determination of Melting Point

Melting point of Pravastatin was found to be in the range of 172° C.

Solubility

Solubility of Pravastatin was determined in pH 1.2, water, & pH 6.8 phosphate buffers. From the above obtained solubility data we can say that 6.8 ph buffer is having more solubility than 1.2 ph buffer (Table 3).

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Pravastatin) and optimized formulation (Pravastatin+ excipients) which indicates there are no physical changes.

The angle of repose of different formulations was ≤ 30.14 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.48g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.56g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.30-15.31 and Hausner's ratio from 1.13-1.18 which reveals that the blends have good flow character.

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (F1 to F6) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm2. This ensures good handling characteristics of all batches.

Disintegration test for core tablets: It was found between 29 – 72 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Drug Content: The percentage of drug content for F1 to F6 was found to be between 89% - 98%. It complies with official specifications.

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (P1 to P5) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of all the formulations ranged between 6 – 7 kg/cm2. This ensures good handling characteristics of all batches.

Thickness: The measured thickness of tablets of all the formulations ranged between 4.26 - 4.92mm. This ensures good handling characteristics of all batches.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

Drug Content: The percentage of drug content for P1 to P5was found to be between 84.15% - 96.02%. It complies with official specifications.

From the *In vitro* drug release studies it was observed that the formulation F7 containing 200mg Carbopol releases maximum drug at the end of 10 hours due to the high polymer concentration and doesn't maintain the lag phase. whereas the formulation F8 containing 200mg ethyl cellulose releases maximum drug at the end of 10 hours due to the higher ethyl cellulose concentration and doesn't maintain the lag phase. whereas F9 containing 100mg of Ethyl cellulose and 100mg of carbopol concentrations maximum drug release was at the end of 9^{th} hour. Whereas F10 containing 50mg of Ethyl cellulose and 150mg of carbopol concentrations maximum drug release was at the end of 8^{th} hour. Whereas F11 containing 150 of Ethyl cellulose and 50mg of carbopol concentrations maximum drug release was at the end of 8^{th} hour.

By comparing the drug release profiles of the formulations F7-F9 the drug release was not lagged upto 5-6 hours with Ethyl cellulose and carbopol. Among all the formulations F10 containing 50mg of Ethyl cellulose and 150mg of carbopol concentrations shows lag time for 6hours and complete drug was released at the end of 8hours. So F10 was considered as the optimized formulation, So the drug release kinetics were performed for the optimized formulation i.e., F10.

From the drug release kinetics of the press coated tablet it was concluded that the formulation F10 maintains lag phase for 6 hours and the drug release was bursted at the end of 7^{th} hour and showed maximum release at the end of 8^{th} hour. It follows zero order release and follows super case II transport mechanism.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Pravastatin for reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood. A satisfactory attempt was made to develop pulsatile system of Pravastatin and evaluated it. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that: Pre-compression parameters and post compression parameters of core and press coated tablets were found to be satisfactory. On the basis of drug content, *in-vitr*o release studies and its kinetic data F3 of core tablet and F10 of coated tablet were selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Pravastatin can be successfully used as a time dependent modified Chronopharmaceutical formulation. Finally from the above results we can conclude that pulsatile drug delivery system of Pravastatin can be formulated using Ethyl celluloe and carbopol.

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