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CHRONOPHARMACEUTICAL RELEASE OF THEOPHYLLINE FROM PULSATILE CAPSULAR DEVICE BASED ON PROGRAMMABLE ERODIBLE PLUG: INFLUENCE OF VARIOUS POYLMERS AND PLUG POSITION

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1.0 Abstract

The objective of this study was development of a chronopharmaceutical capsule drug delivery system capable of releasing drug after pre-determined time delays and studying the influence of various biodegradable polymers and position of plug on lag time. Erodible plugs were prepared by direct compression followed by placing the pellets in the capsule. The theophylline pellets were prepared in four batches with PVP K30, water as binder solution and evaluated for the surface morphology, particle size, drug content and in- vitro release profile and from the obtained results; one best formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The lag time prior to pulsatile drug release correlated well with erosion properties of the plugs and, besides the composition of the plug, could be controlled by the thickness of the plug. The position of the plug also significantly influenced the lag time. Programmable pulsatile release has been achieved from a capsule device over a 2–36 hr period, consistent with the requirement of chronopharmaceutical drug delivery.

1.1 Keywords: Theophylline, hydrogel polymers, Chronopharmaceutical delivery , Pulsatile

1.2 Introduction:

The pulsatile effect i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time[1]. Such systems are also called time-controlled as the drug released is independent of the environment. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount [2-5]. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behavior; drugs having specific absorption site in GIT, targeting to colon; and cases where night time dosing is required.For several drugs or therapies, a pulsatile release profile, where the drug is released completely after a defined lag time, is advantageous[6] : for drugs which develop biological tolerance, for drugs with an extensive first pass metabolism, for drugs targeted to a specific site in the intestinal tract, e.g. to the colon, protecting the drug from degradation and for the adaptation of drug needs to circadian rhythms of body functions or diseases[7-9]. With eroding or dissolving systems, a potential problem is the retardation and therefore there is no immediate drug release after the loss of the barrier function or a premature release, seen in particular with highly water-soluble drugs[10-12]. Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 hrs Asthma is one such disease where pulsatile drug delivery system can be useful[13-15].

The objective of the present study was conceptualized to develop and evaluate the effect of various polymers on the lag time of hydrogel plug of pulsatile drug delivery system consisting of a drug-containing impermeable gelatin capsule, a swelling layer and an insoluble polymeric coating. The lag time was controlled by the hydration/expansion of the swelling layer and subsequent complete rupturing of the various polymer coating, allowing a fast drug release[16-20].

1.3 MATERIALS AND METHODS

1.3.0 Materials

The following chemicals were obtained from commercial suppliers and used as received: Theophylline (Cipla, Bangalore, India), PVP K30 (Dr Reddy's Pvt. Ltd., Hyderabad), Crosspovidone XL-10 (International Specialty Inc, Hyderabad),Ethyl cellulose, Lactose, Formaldehyde solution(Bharat Institute of Technology-Pharmacy, Hyderabad), Xanthan gum and Veegum (Al-ameen College of Pharmacy, Bangalore), Gum Kondagogu and Karayagum (AP Girijan Cooperative Society) ,Hard gelatin capsules, Tween 80 (AP Pharma distributors, Hyderabad), Dichloromethane, High density polyethylene, Phosphate buffer saline, Polydimethylsiloxane, Isopropyl alcohol (S D Fine Chemicals ltd, India).

1.3.0 Methods

1.3.1 Preparation of complete pulsatile system:

Theophylline was pulverized and drug excipients (mixture of theophylline, aerosil and sugar powder) were passed through a 120 mesh screen. Then the above drug and excipients mixture were blended for 15 minutes in a double cone blender (Sreenex machines Pvt ltd,Hyderabad). PVPK-30 was added in water and stirred well still to get a clear solution. Basic core sugar pellets were transferred into coating pan (Bectochem Consultants & Engineers Pvt., Ltd, Hyderabad). Theophylline blend was added slowly by spraying the binder. The pellets are then dried in a tray drier at about 45^0 C-55^0 C to attain the moisture content less than 2.5%. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. The drug and excipients were sieved (315 µm), blended in a Turbula-mixer (IISC, Bangalore) for 15 mins. The bodies and caps of formaldehyde treated hard gelatine capsules were separated manually. Pellets equivalent to 400 mg of theophylline were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the pellets were then plugged with various polymers, i.e., Xanthan gum, Crosspovidone XL-10, Veegum, Karaya Gum and Gum Kondagogu. The plugs were prepared by direct compression method with a single punch press with varying compression pressures. A suspension of magnesium stearate in isopropyl alcohol was used as an external lubricant to avoid sticking of the pellets to the punches. The diameter of the compressed plugs was 6 mm, the weight was 300 mg and the hardness were 40, 80 and 120 N i.e., each polymer weighed 300mg was directly compressed with 3 different compression pressures. The compressed plugs (F1-F45) as shown in **Table no.1** made of various polymers like

Xanthan gum, Crosspovidone XL-10 and Carrageen or Veegum and Gum Kondagogu with dip coating and without dip coating with different compression pressures were placed by hand on top of the pellets in the open end of capsule. Then the caps was then replaced and were completely coated by dip coating method with 5% ethyl cellulose ethanolic solution.

Table no-1: Composition materials of various polymers plugs and percentage of coating used.

Batch code	Plug polymer material	Ratio of plug Polymer : Filler (mg)	Ethyl cellulose-Ethanolic coating solution (%)
F1	Xanthum Gum (XG)	300 : 0	nil
F2	XG	200 : 100	nil
F3	XG	150 : 150	nil
F4	XG	300 : 0	2.5%
F5	XG	200 : 100	2.5%
F6	XG	150 : 150	2.5%
F7	XG	300 : 0	5.0%
F8	XG	200 : 100	5.0%
F9	XG	150 : 150	5.0%
F10	Cross Povidone (CP XL-10)	300 : 0	nil
F11	CP XL-10	200 : 100	nil
F12	CP XL-10	150 : 150	0%
F13	CP XL-10	300 : 0	2.5%
F14	CP XL-10	200 : 100	2.5%
F15	CP XL-10	150 : 150	2.5%
F16	CP XL-10	300 : 0	5.0%
F17	CP XL-10	200 : 100	5.0%
F18	CP XL-10	150 : 150	5.0%
F19	Karaya Gum (KG)	300 : 0	nil
F20	KG	200 : 100	nil
F21	KG	150 : 150	nil
F22	KG	300 : 0	2.5%

F23	KG	200 : 100	2.5%
F24	KG	150 : 150	2.5%
F25	KG	300 : 0	5.0%
F26	KG	200 : 100	5.0%
F27	KG	150 : 150	5.0%
F28	Gum Konda Gogu(GKG)	300 : 0	nil
F29	GKG	200 : 100	nil
F30	GKG	150 : 150	nil
F31	GKG	300 : 0	2.5%
F32	GKG	200 : 100	2.5%
F33	GKG	150 : 150	2.5%
F34	GKG	300 : 0	5.0%
F35	GKG	200 : 100	5.0%
F36	GKG	150 : 150	5.0%
F37	Veegum (VG)	300 : 0	nil
F38	VG	200 : 100	nil
F39	VG	150 : 150	nil
F40	VG	300 : 0	2.5%
F41	VG	200 : 100	2.5%
F42	VG	150 : 150	2.5%
F43	VG	300 : 0	5.0%
F44	VG	200 : 100	5.0%
F45	VG	150 : 150	5.0%

1.3.2 Drug -excipient compatibility studies:

Compatibility studies were performed using FTIR spectrophotometer (Shimadzu, Japan). The FTIR spectrum of pure drug and physical mixture of drug and excipients were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum.

1.3.3 Drug -Polymer Compatibility Studies by DSC:

Physical mixture of the drug theophylline and various polymers were prepared. After powder sieving, the mixture was analysed by DSC. The thermogram obtained was compared with the thermogram of the pure drug.

The instrument was calibrated using indium standards. Accurately weighed samples (10mg) were hermetically sealed in flat bottom aluminum pans. The scanning was carried out at a temperature ranging from 40^0C to 300^0C at a rate of 20^0C/min under an atmosphere of nitrogen[22-24].

1.3.4 X-Ray Diffraction study:

Powder X-ray diffraction patterns where traced employing X-ray diffractometer (Seiferd,Model NO.3000,Germany) for samples, using Ni filtered CuK radiation , a voltage of 40 KV, a current of 30mA radiation scattered in the crystalline regions of the sample was measured . patterns where obtained by using a step width of 0.04 ºC with a detector resolution in 2θ (diffraction angle) between 10º and 80º at ambient temperature[25].

1.3.5 Determination of absorption maxima:

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 272nm. Hence all further investigations were carried out at the same wavelength.

1.3.6 Determination of drug content in pellets:

In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 6.8. The flask was shaken for 12 hrs using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 272 nm by using UV absorption spectroscopy.

1.3.7 Determination of Particle size and external morphology:

Determination of average particle size of theophylline pellets was carried out by optical microscopy (Scanning Electron Microscope (SEM) studies were carried out by using JEOL JSM T-330 'A' Scanning microscope (Japan). Dry pellets were placed on an electron microscope brass stub and coated with gold in an ion sputter. Picture of microcapsules were taken by random scanning of the stub.

1.3.8 Determination of the time of erosion of the plugs: The time for complete erosion of the plugs (compressed plugs) was determined with a disintegration testing apparatus (Cintex Industrial Corporation, Dadar, Mumbai), (900 ml pH 6.8 phosphate buffer USP XXIII, 37 ± 0.5^0C).

1.3.9 Determination of swelling index of plugs: The plugs prepared with varying compression pressures were tested for swelling index using disintegration apparatus (900 ml pH 7.4 phosphate buffer USP XXIII, 37±0.5 ˚C C). Xanthan gum polymer was taken as model polymer in order to determine swelling rate[26-28].

1.3.10 In vitro release profile of pulsatile capsule:

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred millilitres of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 ◦C. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analysed at 272 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

1.3.11 Position of the plug in the insoluble capsule body

From each polymer batch, one formulation having optimum lag time i.e., around 6 hrs was selected and investigated for the effect of plug position in the insoluble capsule body. The polymer plug was positioned at two different places i.e., in first formulation the plug is placed at 3 mm below from the surface of the capsule and in second formulation the plug is placed such that after placing the plug in the capsule body, 3 mm of the plug is remained above the surface of the capsule opening. Formulations F2, F16, F21, F31 and F43 were selected and designated as F2A & F2B, F16A & F16B, F21A & F21B, F31A & F31B and F43A & F43B respectively. The formulations designated with letter ‘A’ was placed 3 mm above the capsule opening surface and formulations designated with letter ‘B’ was laced 3 mm below from the opening surface of capsule body.

1.3.12 In vitro release profile of pulsatile capsule

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used & referred to as sequential pH change method[29-31]. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 ◦C. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 272 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

1.3.13 Results and discussion

The effect of various parameters of the plug (type of material, thickness and hardness) and the capsule content (type of excipient, effervescent agents) were investigated in order to characterize the lag time prior to drug release and the drug release profiles of the capsules. The plugs were formed by direct compression method with a single punch press with varying compression pressures, the meltable plugs were prepared by melting and pouring the melt into a mould. Theophylline pellets were prepared by direct compression method followed by placing the pellets in the capsule body by hand filling and placing the plug on the capsule opening. A tight fit between the plug and the impermeable capsule was very important in order to prevent water penetration to the capsule content and drug release prior to complete erosion of the plug material. In order to identify proper plug materials, they were tested for swelling index using disintegration apparatus. It was found that the principle peaks of theophylline are intact in the formulations. FTIR graph showed that drug-excipients interactions were not observed as shown in **Fig no-1**. This indicates that the drug was compatible with the formulation components. DSC studies were performed on the drug and polymers alone and on freshly prepared Co-ground and physical

mixtures in order to study the interaction between pure drug and polymers. The DSC thermograms of pure drug and the physical and co-ground mixtures showed two endothermic peaks. First broad endothermic peak in the range of 500c-1300c corresponds to polymeric endothermic peak, second endothermic peak represents the melting temperature of drug in mixtures. X-Ray diffraction studies were undertaken to consolidated DSC data indicating reduction of crystallinity of theophylline with other polymers). Therefore, X-Ray diffraction pattern of pure theophylline, physical mixtures of theophylline with various polymers in 1:2 ratio were observed. The diffraction spectrum of pure theophylline indicates that the drug is amorphous in nature as shown in **Figure no- 2**. X-ray diffraction pattern of drug with polymers also showed no sharp peaks indicating its amorphous nature of the mixture. A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 272nm. Hence all further investigations were carried out at the same wavelength. The percentage drug content in second batch (TP2) was found to be highest i.e., 99.3% and in the fourth batch (TP4) the percentage drug content was the least i.e., only 89%. In TP1 and TP3 it was found to 93.6% and 95.9% respectively. Hence TP2 batch was selected for the fabrication of pulsatile drug delivery system. The SEM photograph of second batch (TP2) was taken to determine the particle size and surface morphology of pellets**.** On the basis of percentage drug content formulation TP-2 was selected as better formulation for designing pulsatile device. In vitro release profiles were found to have very good sustaining efficacy. After coating thickness of the plug was increased up to 2-3mm all the designed pulsatile capsules were found to be in the limit of weight variation test. The formulation F1 showed a lag time of about 8 hrs while the lag time of F2 was decreased to 6 hrs because of less amount of polymer in the plug on the other hand lag time of F3 was further decreased to 4 hrs this might be probably due to the effect of high content of filler and less amount of polymer in the plug. The 2.5 % EC coating on F4, F5 and F6 plugs has shown an increase in lag time about 2 hrs. The effect of 2.5 % coating and filler content on the plugs F5 and F6 has not been noticed as the difference in lag time was less than 2 hrs. On the other side 5% EC coating of F7, F8 and F9 further increased the lag time and the plugs were ejected at the end of 12, 16 and 20 hrs. formulations F10, F11 and F12 released the drug immediately, no lag time was observed, on the other hand 2 hrs lag time was observed for formulations F13 and F14 i.e., at the end of 2^{nd} h 76.2%, 97.5% while F15 ejected the plug at the end of 2 h, this might be due to high filler

concentration. With F16 the lag time was about 6 hrs and the lag of F17 was found to be 4 hrs while a increase in the expelling power of plug F18 has been noticed as it showed the least lag time of only 2 hrs, less polymer content and high amount lactose might be the cause for the decrease in lag time. The lag time achieved with the formulation F19 was 12 hrs on the other formulations F20 and F21 ejected the plugs well before 12 hrs, this might probably due to the effect of lactose as it enhances the absorption of media, while the 2.5% EC coated plug F22 remarkably achieved a lag time of 28 hrs and lag time for formulations F23 and F24 was decreased by 8 hrs because of less concentration of polymer content in the plugs. The 5% EC coated plug formulation F25 displayed highest lag time of 36 hrs on the other hand F26 and 27 exhibited a lag time of 28 hrs which is 8 hrs less when compared with F25. Formulations F29 and F30 not much lag time was achieved as the plugs ejected well below 2 hrs this is due to rapid absorption of dissolution medium by lactose present in plugs as shown in **Fig no-3**. The effect of 2.5% EC coating on formulations F31, F32 and F33 has increased the lag time by 2 hrs. the 5% coating of EC on plug F34 increased the lag time up to 10 hrs when compared with uncoated plug F28 which achieved a lag time of only 2 hrs while the formulations F35 and F36 showed a lag time of 6 hrs which is 4 hrs more when compare with F28 and F29 respectively not much lag time was achieved with the formulations F37, F38 and F39 as the plugs ejected out well before 2 hrs, as the polymer alone itself was very rapidly swelling the effect of filler was not observed. The 2.5 % EC coating on F40 has cause little increase in lag time where the plug ejected out before 4 h on the other side the effect of 2.5% EC coating on F41 and F42 did not show any effect as the plugs ejected out well before 2 hrs but the 5% ethyl cellulose coating on F43 has achieved a lag time of 6 hrs which is highest lag time when compared with all other formulations of Veegum polymer. In case of F44 the plug ejected out within 4 hrs showing a lag time less than 4 hrs. The effect of 5% EC coating on F45 was not seen as the plug ejected out well before 2 hrs showing a lag time less than 2 hrs. On the basis of in-vitro dissolution studies it was found that in all cases the plugs which were placed 3 mm above the body surface, the plug ejected 2- 4 hrs earlier decreasing the lag time. It was clearly observed that, in all the cases where the plug was placed 3 mm below the surface level of capsule body, showed a delay of lag time ranging from 2- 12 hrs.

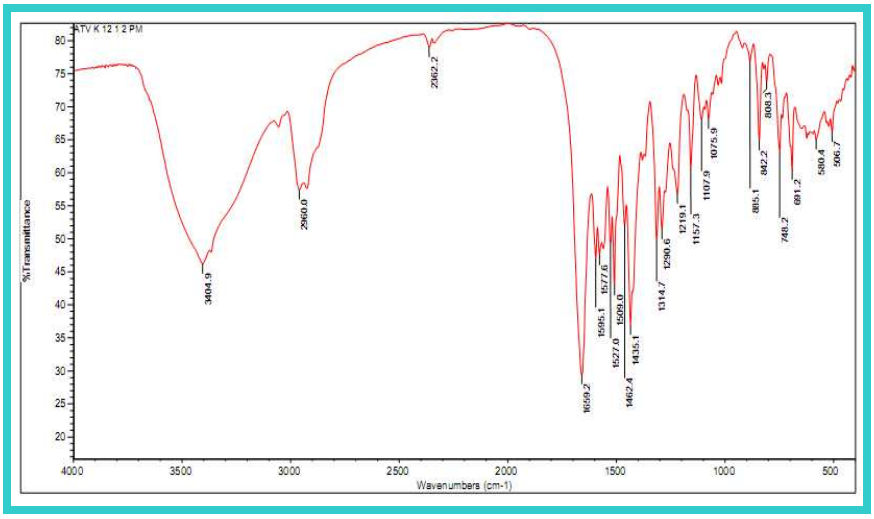

Fig no-1: FTIR of pure drug theophylline with all excipients

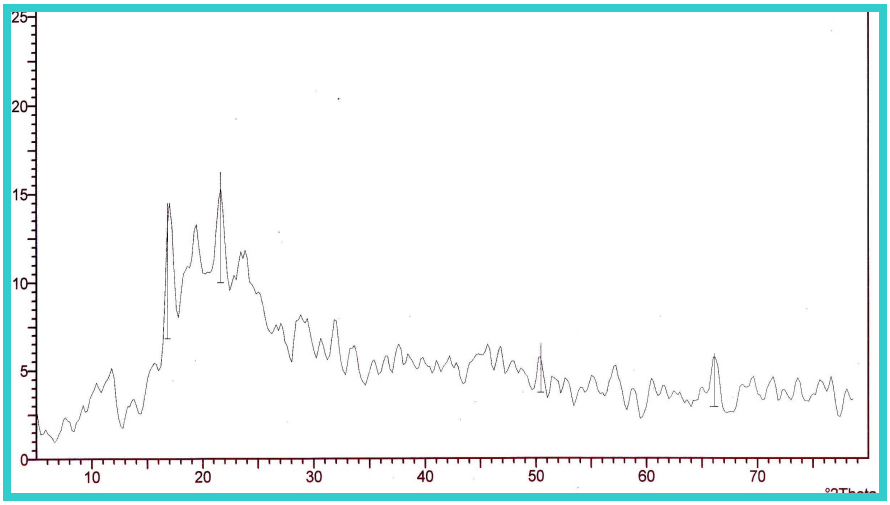

Fig no-2: X-ray diffraction (XRD) of pure drug theophylline

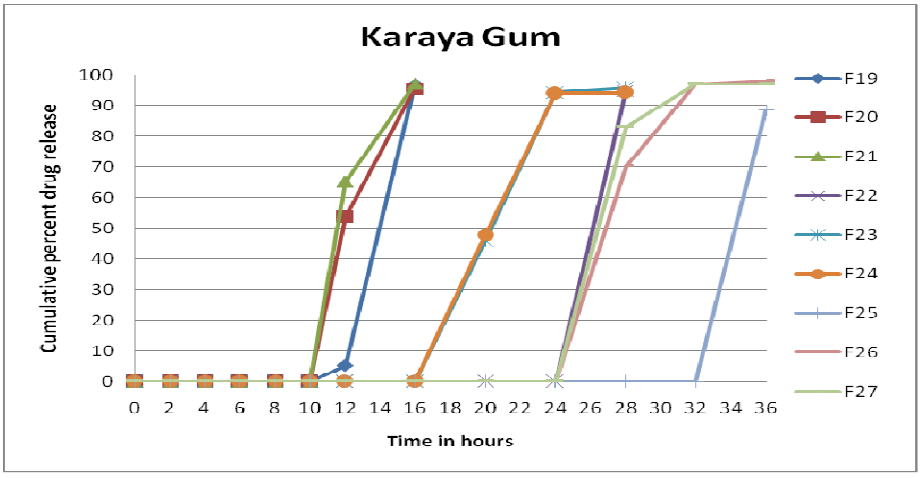

Fig no-3: Comparative dissolution profiles of various Karaya Gum polymer plugs

1.3.14 Conclusion:

In conclusion, the results suggested that pulsatile release is dependent on all the parameters and found that position of the plug in the capsule body significantly affects lag time. It is evident that an increase in the polymer concentration in the plug results in an increase in lag time and drug release from the system. This hybrid system exhibited pulsatile release, a feature offering significant advantages for certain therapies. The characteristics and properties, depending on the nature of the materials employed, considerably influence the function of the system and release mechanisms, as does their swelling ability. Finally, it is possible to release a drug over a predetermined period of time with specific release rates by manipulating the polymers used to prepare plugs.

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