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Development of Oral Sustained Release Tablets of Theophylline

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ABSTRACT

The use of rapid release oral theophylline preparations have been declined due to the higher incidence of side effects resulting from rapid absorption. The aim of this experiment is to investigate processed jackfruit latex as a natural tablet retardant polymer in the development of oral sustained release tablets of theophylline . The resin of *Artocarpus Hetrophyllus* was isolated from the peduncle of jackfruit. The procedure for isolation and processing is very simple. The resin showed hydrophobic nature. The granules prepared showed good flow property and compressibility. All the fabricated tablets passed standard evaluation tests. The optimised formulation showed an extended drug release for a period of 10 hours. For comparison, matrix tablets of theophylline with Kollidon SR were also formulated and the level required for a drug release profile identical to that of the optimized formulation was also determined. The tablets also showed good stability when subjected to short term stability studies. Hence it can be concluded that processed jackfruit latex can be used as a natural inexpensive hydrophobic polymer in the formulation of oral sustained release tablets.

Keywords: theophylline, sustained release, processed jackfruit latex, Higuchi model.

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INTRODUCTION

The xanthine drugs, especially theophylline and its derivatives are thought to be the most useful bronchodilators for moderate or severe reversible bronchospasm [1]. Theophylline has a narrow therapeutic index and must maintain plasma levels within a well defined therapeutic range to be effective. It has a short half life. An oral sustained release formulation can reduce fluctuation in plasma concentration and allow longer dosing intervals [2].

A matrix tablet is the simplest method of developing a sustained release dosage form. In plastic matrix tablets the active ingredient is dispersed in an inert plastic polymer matrix by either particle or molecular dispersion and the possible mechanism of release of drug in such type of tablet is diffusion. In the recent period, there is increased interest in natural polymeric substances whose advantages consist in safety, compatibility with biological fluids, easy availability and a relatively low price. The use of natural polymers and their semi synthetic derivatives in drug delivery continues to be an area of active research despite the advent of synthetic polymers. The jackfruit latex is a sticky white substance which is physically found to be hard. The latex obtained from the peduncle of the Jackfruit was studied and found to be a promising candidate as a coating polymer for mucoadhesive microsphere [3]. Shende Pravin et.al, developed a formulation of w/o/w multiple emulsions of sodium salicylate with processed jack fruit latex as primary emulsifier. Better stability and a controlled drug release was obtained with 10%w/w processed jack fruit latex as emulsifier [4].

The objective of this study is to investigate processed jackfruit latex as a natural tablet retardant polymer for the development and optimization of an oral sustained release formulation of theophylline. The processed Jackfruit latex powder is also tested for its stability and its suitability for direct compression. The scientific name of jackfruit is *Artocarpus heterophyllus* belonging to the family Moraceae. It is planted erratically as a backyard crop and usually left to grow requiring not much attention. Its local accessibility is an added advantage as it grows abundantly in Kerala.

Kollidon SR is Polyvinyl acetate and povidone based matrix retarding agent. It is particularly suitable for the manufacture of pH –independent sustained release matrix tablets [5]. It is a free flowing powder insoluble in water. The excellent flowability and compressibility of Kollidon SR makes this excipient particularly suitable for the manufacture of sustained release tablets obtained by direct compression. Kollidon SR has a unique character of maintaining tablet geometric shape until the end of dissolution test, this is mainly due to its major component, the water insoluble PVA while the minor water soluble part PVP is responsible for the pore formation causing diffusion controlled release mechanism [6]. The required content of Kollidon SR in the tablet depends on the solubility of the active ingredient. For drugs which are very slightly soluble to practically insoluble in water, 15-25% of polymer is required to formulate a sustained release tablet while for sparingly soluble to slightly soluble drugs 25 -40 % of polymer is needed. For soluble to freely soluble drugs 40-55% of polymer is required to develop a formulation with sustained release during 12-24 hours. Safiqul Islam et al studied the invitro release kinetics of diltiazem hydrochloride from matrices of waxy materials

(Carnauba wax, bees wax, cetyl alcohol and glyceryl monostearate) alone or in combination with Kollidon SR. Initial burst release was observed in case of waxy granules. Tablets prepared in combination of waxy granules and Kollidon SR sustained the drug release for more than 12 hours [7]. In this experiment, an attempt is done to determine the amount of Kollidon SR that gives a comparative drug release profile as that of the optimized tablets containing natural processed jackfruit latex powder. The release mechanism of the drug from these matrices are also explored and explained with the help of suitable kinetic models.

MATERIALS AND METHODS

The following materials were used. Theophylline I.P (Bangalore organics, Kakkavayal, Kozhikode), Lactose I.P (Bangalore Organics, Calicut), Kollidone SR (Kawarlal excipients, Chennai). The other materials used for formulation and analysis like talc, magnesium stearate, Disodium hydrogen phosphate, potassium dihydrogen orthophosphate, hydrochloric acid etc were of pharmaceutical/ analytical grade.

Collection and processing of jackfruit latex

The latex was collected from the peduncle of the slightly under ripe jackfruit. The latex was collected in a clean 250 ml beaker containing 50 ml demineralised water. About 200 ml was collected in one go. The diluted latex started coagulating. The coagulated mass was washed with demineralised water several times to free it from the extraneous water soluble plant materials. The finally washed rubbery latex was dried under vacuum and stored in desiccators. At the beginning the latex appears white which changes to off white on storage. The dried latex was powdered with the help of pestle and mortar and dissolved in acetone. Then this solution was filtered to remove all insoluble organic and inorganic matters. The filtered solution was then spread on a glass petridish for solvent evaporation and allowed to dry completely under vacuum to get yellowish white powdery but slightly sticky mass. This was then spread on a watch glass and maintained at a temperature of 120 °c in a hot air oven for 2 hours. The residue was then cooled and allowed to dry completely under vacuum to get a yellowish white solid mass. The solid mass was powdered and transferred into a tightly closed container. This powder was used as a natural release retardant polymer in the formulation development of sustained release matrix tablet [8].

Tests for suitability for direct compression

To predict the flow properties of the latex powder, the following parameters were determined. Hausner ratio, Carrs compressibility index and angle of repose of the powder samples were determined.

Hausner ratio [9]: determined by the equation

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{poured density}}$$

A ratio greater than 1.25 is considered to be an indication of poor flowability.

Carrs compressibility index: Determined by the equation

Carrs compressibility index (%) = $(\text{Tapped density} - \text{Bulk density}) \times 100 / \text{Tapped density}$

A value greater than 25 indicates poor flow; a value below 15 indicates good flow

Angle of repose: The angle of repose of the latex sample was determined by fixed funnel method.

A value less than 24 indicates excellent flow ability; 25-30 shows good flow; 30-40 is passable limit and a value above 40 indicates poor flow property.

Preformulation studies

The drug and the polymers were kept in 1:1 proportion and kept at a temperature of 40°C and 75% relative humidity. The mixture was analysed periodically at intervals of two weeks for any changes in colour, texture or odour development and assay of active ingredients. The flow properties of the granules prepared as per Table I were also studied by determination of parameters like Carrs index, Angle of repose and Hausner ratio.

Preparation of matrix tablets of theophylline using jackfruit latex

Theophylline, Dicalcium Phosphate, and jackfruit latex powder were mixed and granulated with acetone. The granules were dried in an oven at 50°C for 30 minutes. After drying, the granules were passed through sieve 22/44 to obtain uniform sized granules. The granules were then lubricated with talc and magnesium stearate. The compositions of the various formulations are shown in table 1.

The prepared granules were then compressed using 8 mm flat punches in a 16 station Cadmach machine.

Preparation of matrix tablets of theophylline using Kollidon SR

Table II shows the compositions of various formulations of theophylline. Matrix tablets containing Kollidon SR. Tablets were prepared by direct compression method. The ingredients were mixed thoroughly and compressed in 8 mm flat punches in a 16 station Cadmach rotary tablet machine.

Evaluation of tablets

Tablets were subjected to various physical tests which include weight variation, thickness, hardness, friability etc as per standard methods. Tablets were also subjected to assay of active ingredients.

In vitro drug release studies

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 10 hours using a 6 station USPXXII type 1 apparatus at $37 \pm 0.5^{\circ}\text{C}$ and 50 rpm speed. The dissolution studies were carried out in triplicate for 10 hours (initial 2 hours with 0.1N HCL and rest 8 hours in phosphate buffer of PH 6.8). The samples were collected at fixed time intervals, filtered and analysed spectrophotometrically after suitable dilution at a wavelength of 271 nm [10].

Data analysis

To analyze the in vitro release data, various kinetic release models were used to describe the release kinetics.

Data treatment

The rate of drug release was calculated from the slope of the Highuchi curve expressed as % drug released / hr $^{1/2}$. The dissolution data were also fitted according to the well known exponential equation (1) which is often used to describe the drug release behaviour from polymeric systems.

$$M_t/M_{\infty} = K t^n \quad \text{-equation 1}$$

where M_t/M_{∞} is the fractional (0.1-0.6) drug release at time t, K is a constant incorporating the properties of the macromolecular polymeric systems and the drug and n is a kinetic constant which is used to characterize the transport mechanism. The value of n for a tablet n =0.45 for Fickian (case I) release, > 0.45 but < 0.89 for non fickian (anomalous) release and 0.89 for Case II type of drug release and > 0.89 for super case II type of release.¹¹ Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport refers to the summation of both diffusion and dissolution controlled drug release.

The difference factor of the drug dissolution profiles and similarity factor are also calculated using equation 2 and 3 respectively [12].

$$\text{Difference factor} = \sum_{j=1}^n \frac{[R_j - T_j]}{\frac{(R_j + T_j)}{2}} \times 100 \quad \text{-equation 2}$$

The difference factor is zero if the profiles are identical and increases proportionally with the dissimilarity between the two dissolution profiles.

$$\text{Similarity factor} = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^n (R_j - T_j)^2 \right]^{-0.5} * 100 \right\} \quad \text{- equation 3}$$

Here, n is the sampling number and R_j and T_j are the % dissolved of the two products at each time points j .

Similarity factor is a logarithmic transformation of the sum squared error of differences between the two products over all time points. When the profiles are identical similarity factor is 100 and tends to zero as dissimilarity increases.

Stability studies

The optimized tablets of Jackfruit latex powder and Kollidon tablets showing similar drug release characteristics were kept for stability studies in a stability chamber at 75% \pm 5% relative humidity and 40 \pm 2^oc. The tablets were taken out at 30 days, 60 days and 90 days from the stability chamber and assayed. Any change in colour, texture or development of odour was also noticed.

RESULTS AND DISCUSSION

Suitability of jackfruit latex powder for direct compression

The processed jackfruit latex appeared as a yellowish white powdery mass whose flow property parameters like Hausner ratio, Carrs compressibility index and angle of repose are shown in Table III. Results of these parameters indicated poor flow property and compressibility. Hence the latex powder was found as not suitable for direct compression.

Preformulation studies

Binary mixtures of the drug and jack fruit latex powder kept for compatibility studies did not show any change in physical appearance, colour change, or odour development. Results of periodic assay of active ingredient also indicate that there is no incompatibility between theophylline and jackfruit latex powder. The granules prepared as per Table I show good flow property and compressibility behaviour as indicated from the Hausner ratio, compressibility index and angle of repose values. The Hausner ratio for all the formulations lie between 1.18 - 1.06; compressibility index between 15-9; and angle of repose found were between 27-35.

Evaluation of tablets

The prepared tablets passed all physical tests which include weight variation, thickness, hardness, friability as per standard methods. Assay of active ingredient was also found to be within the limit. Tablets prepared with higher % of latex powder was found extremely hard and showed tendency to cap.

Preparation and evaluation of matrix tablets with kollidon sr

In the initial stages of this work, preliminary trials were carried out to short list the levels required for optimization studies. Since theophylline is a slightly soluble drug, about 25-40% of polymer would be required for good sustained release. For comparative study with the natural polymer, polymer composition from 2.5 % onwards was tried, but tablets of acceptable physical parameters were obtained from 10% and above polymer content. Therefore, compositions less than this was excluded from further study. Formulations with 10% and above polymer content passed all physical tests and assay of active ingredients.

Drug release testing and kinetics of drug release

Results of in vitro drug release studies of formulations FLX1-FLX7 are shown in Fig 1 & 2. Of these, formulation FLX4 containing 10% jackfruit latex showed a drug release of 83.63 % in 10 hours. Formulation containing lesser percentage of latex showed lesser duration of drug release. With higher percentages of latex the duration of drug release was prolonged but the cumulative percentage of drug released was less. Fig 3, 4, & 5 give the drug release profiles of FK4-FK15 containing Kollidon SR matrix release retardant. Formulation FK4 containing 10% of the polymer released 97.5% of the drug in 30 min. The % of polymer was gradually increased to prolong the release of drugs. It was found that Formulation FK15 containing 37.5% of Kollidon SR give a drug release profile that is comparable to FLX4 containing 10% jackfruit latex powder.

The rate of drug release was calculated from the slope of the Higuchi curve for the optimized jackfruit latex powder tablet and the Kollidon SR tablet FK15 (Fig 6 & 7). Fig 8 & 9 show the dissolution data fitted into Korsmeyer-Peppas model indicating the mechanism of drug release mainly by diffusion. The difference factor and similarity factor between the two formulations give a better comparative data of the dissolution profiles of Jackfruit latex powder tablet optimized and the Kollidon SR tablet containing 35% of Kollidon. The value of n obtained for FLX4 was found to be 0.4105 indicating drug releases predominantly by drug diffusion for jackfruit latex tablets. The value for release exponent for Kollidon SR tablets is 0.3457 which is beyond the limits of Korsmeyer model so called power law. The power law can give only limited insight into the exact release mechanism of the drug and it appears to be a complex mechanism of diffusion and erosion [13]. Values of various release parameters for Higuchi model and Korsmeyer Peppas model are indicated in Table IV.

The drug release profile of FLX 4 and FK 15 are compared by calculating the similarity factor and difference factor as per equation 2 & 3. The value obtained for difference factor is 3.29 and similarity factor obtained is 94.58 indicating identical dissolution profiles for FLX4 and FK15.

Stability studies

The drug content in both the formulations were within limit throughout the stability study period. While the Kollidon tablets remained intact, a slight discolouration was developed

in Jackfruit latex tablets suggesting extra precautions in storage requirements like packaging in an airtight container and protection from light.

Table 1 Composition (mg/tablet) of theophylline matrix tablets containing jackfruit latex

Formulation	Drug	Jackfruit latex powder	Dicalcium Phosphate	Talc	Magnesium stearate	Total wt of the tablet
FL1	100	5	91	2	2	200
FL2	100	10	86	2	2	200
FL3	100	15	81	2	2	200
FL4	100	20	76	2	2	200
FL5	100	25	71	2	2	200
FL6	100	30	66	2	2	200
FL7	100	35	61	2	2	200

Table II Composition (mg/tablet) of theophylline matrix tablets containing Kollidon SR

Formulation	Drug	Kollidon SR	Dicalcium Phosphate	Talc	Magnesium stearate	Total wt of the tablet
FK1	100	5	91	2	2	200
FK2	100	10	86	2	2	200
FK3	100	15	81	2	2	200
FK4	100	20	76	2	2	200
FK5	100	25	71	2	2	200
FK6	100	30	66	2	2	200
FK7	100	35	61	2	2	200
FK8	100	40	56	2	2	200
FK9	100	45	51	2	2	200
FK10	100	50	46	2	2	200
FK11	100	55	41	2	2	200
FK13	100	60	36	2	2	200
FK14	100	65	31	2	2	200
FK15	100	70	26	2	2	200

Table III Flow property and compressibility of processed jackfruit latex powder (n=3)

Hausner ratio	Compressibility index (%)	Angle of repose (o)
1.34±.02	25.39±.14	47.35±2.5

Table IV Drug release parameters

Formulation	Higuchi model		Korsmeyer Peppas model		
	release rate (h-1/2)	R2	Release rate (h -n)	n	R2
FLX4	26.066	0.9907	0.3676	0.4105	0.9969
FK15	26.132	0.9884	0.3658	0.3457	0.9945

Cumulative % of drug released

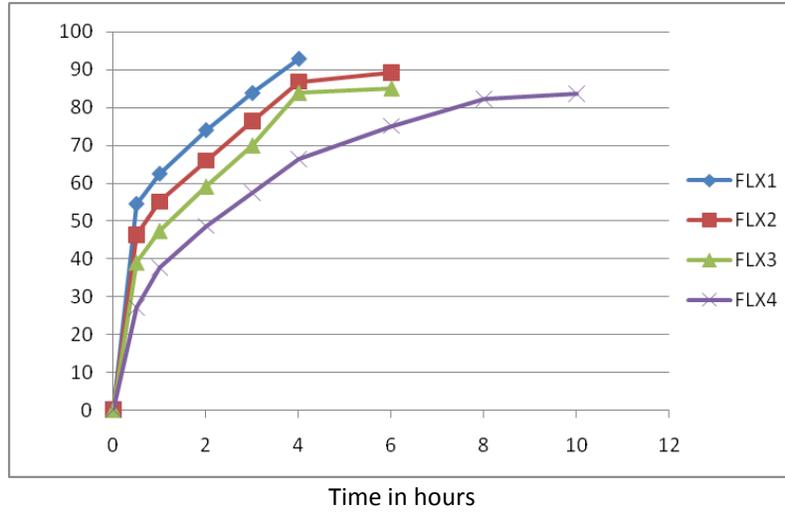


Fig 1

Cumulative % of drug released

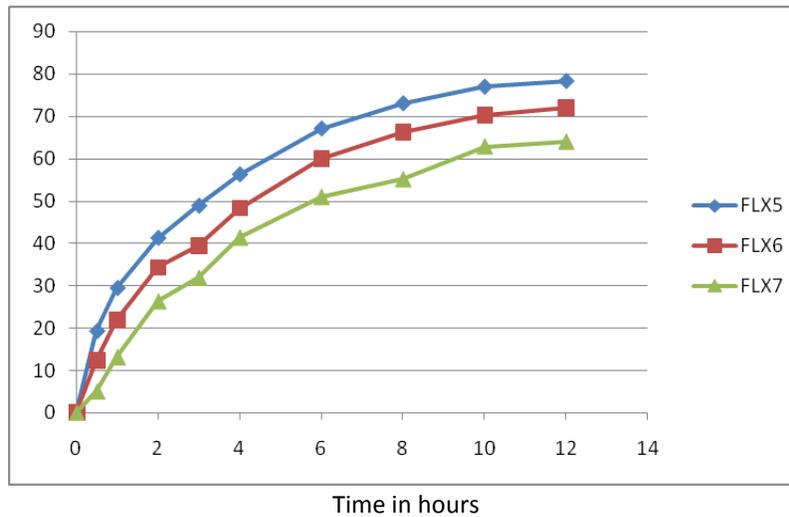


Fig 2

Cumulative % of drug released

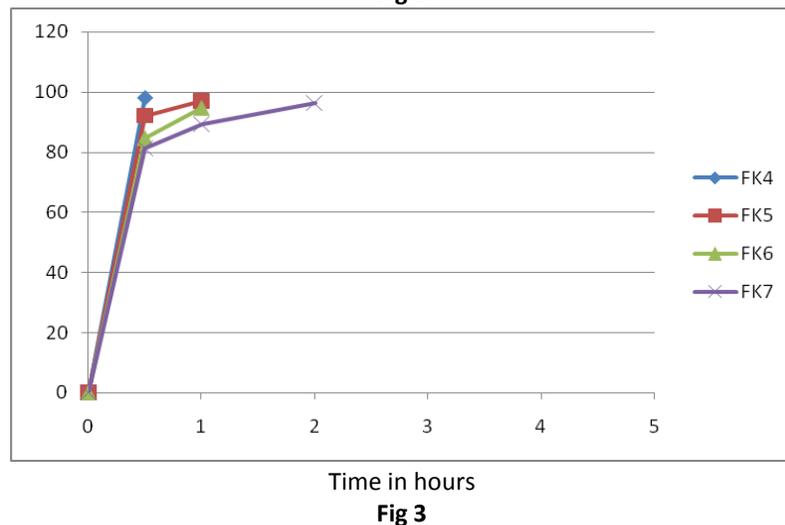
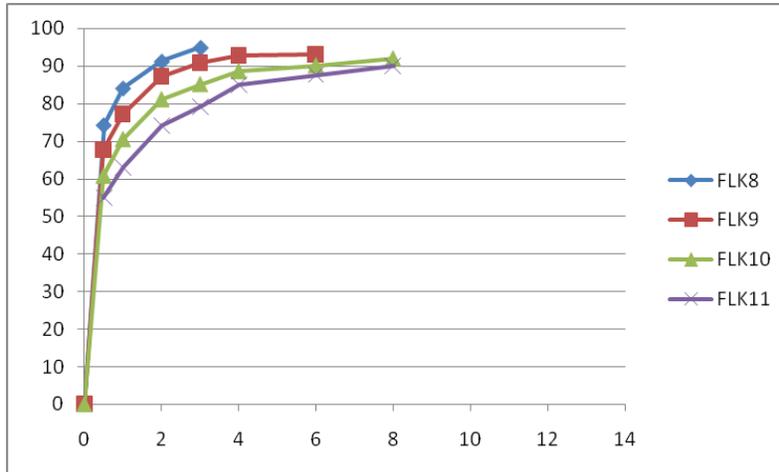


Fig 3

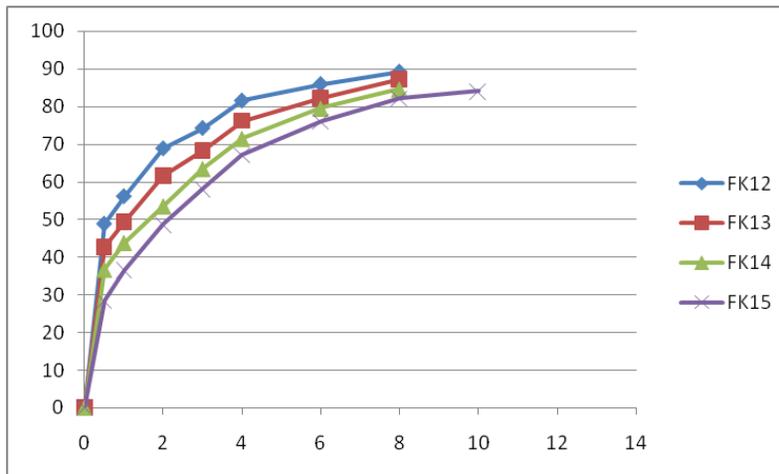
Cumulative % of drug released



Time in hours

Fig 4

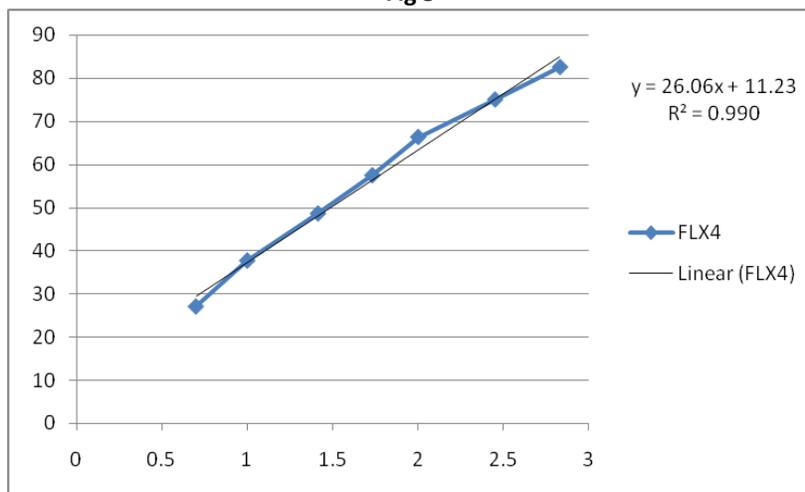
Cumulative % of drug released



Time in hours

Fig 5

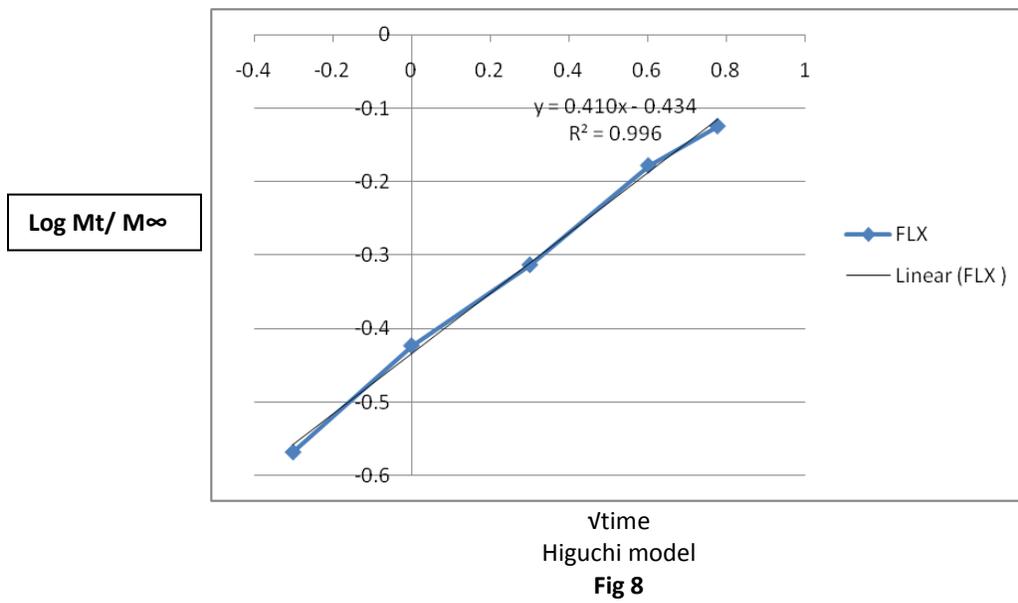
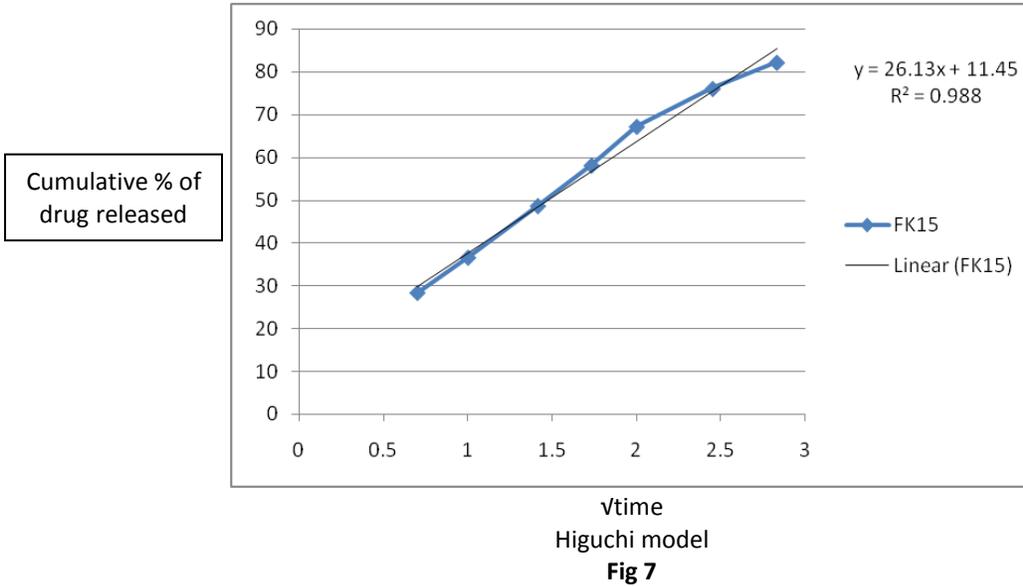
Cumulative % of drug released

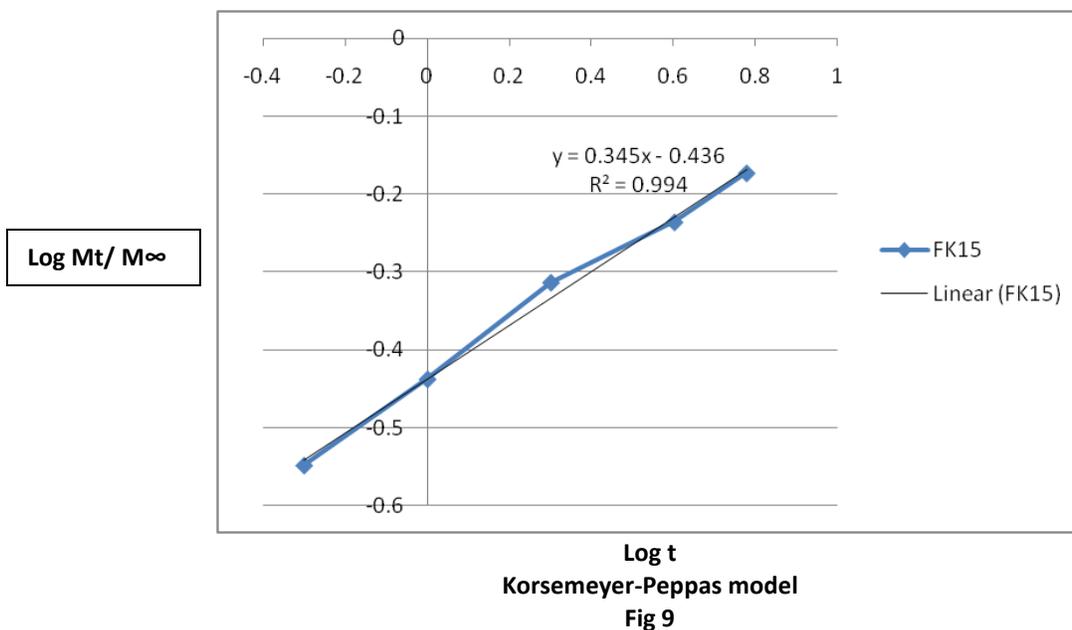


sqrt(time)

Higuchi model

Fig 6





CONCLUSION

Sustained release tablets of theophylline containing Jackfruit latex powder as release retardant was formulated. The optimization of the level of matrix retardant in the formulation was done based on data from in vitro drug release studies. It was found that 10% of jackfruit latex powder was required for optimum drug release profile. For comparative study, sustained release matrix tablets of theophylline containing Kollidon SR were also developed. It was found that tablets containing 35% of Kollidon SR gave a drug release profile identical to that of 10% Jackfruit latex powder. The dissolution was found to follow Higuchi model of drug release kinetics.

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