WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 6, 2076-2092. Research Article ISSN 2277– 7105

DESIGN AND DEVELOPMENT OF MICROBIALLY TRIGGERED ZIDOVUDINE TABLETS IN COLON CANCER

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Article Received on
17 April 2016,

Revised on 08 May 2016,
Accepted on 29 May 2016

DOI: 10.20959/wjpr20166-6444

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ABSTRACT

The main objective of this study was to target zidovudine to the colon for improvement of exploited immunity by HIV infection using microbially triggered approach. Zidovudine is an antiretroviral drug which falls under the category of nucleoside reverse transcriptase inhibitor. Sodium starch glycolate (SSG) was also used for controlling drug release in such a manner that it can provide effective control over sustained release of drug. The matrix tablets were coated with enteric polymers as Eudragit L100 and Eudragit S100 in 1:1 ratio for controlling upto 12 hrs drug release in colon. The tablets were prepared by wet granulation method. Pre-formulation and micrometric studies of the drug, polymer & physical mixture were carried out. The results of pre-formulation studies were in accordance with reported literature values. Various in vitro tests like hardness, friability, weight variation, content uniformity, dissolution and disintegration were performed. Comparing the release profiles of formulations, under different pH conditions, influence of speed and concentration of super-disintegrant on the rate and extent of drug release was evident. It was also clear from the result that the drug release was faster in MF 22 but the effect of rat caecal content was more pronounced in case of MF 12. However MF 22 formulation batch has 96.45 % while MF12 formulation shows 94.02 % at stimulated intestinal pH. From the results of the data fitting to four different kinetic models, the best linearity was shown by zero order models giving value of r^2 much closer to 1.. Value of "n" was found to lie between 0.67 - 0.87 indicating anomalous behavior (also called as non-fickian diffusion) as a mechanism of drug release. This consists of phenomenon of diffusion and erosion of polymer matrix

KEYWORDS: Microbially triggered, Guar gum, Xanthan gum, Eudragit S100, Eudragit L100

INTRODUCTION

Development of colon drug delivery system through oral route has achieved the most attention and success in the recent years to achieve higher drug release control.[1] Drug-loaded carriers that are specifically degraded by colonic bacteria can be targeted to the colon provided the colon contains over 400 distinct species of bacteria having a population of 10^{11} to 10^{12} CFU/mL with bacterioids, Bifidobacterium, Eubacterium and lactobacillus being abundantly present than other species.[2] Colon bacteria produces variety of enzymes such as β-glucuronidase, β-xylosidase, α-arabinosidase, β-galactosidase, nitroreductase, azoreductase, deaminase, urea hydroxylase etc. These bacteria survive in the colon by digesting the various types of substrates that remained undigested in the small intestine region.[3]

Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a polysaccharide-based delivery system for colon is presence of high levels of polysaccharidases of microbial origin in the human.[4]

Drug release retarding polymers are the key performers in matrix systems and various polymers have been investigated as drug retarding agents, each presenting a different approach to the matrix system.[5]

Natural polysaccharides like guar gum and xanthan gum were used as a matrix forming agents for microbially triggered approach. Guar gum is a galactomannan (polysaccharide consisting of mannose backbone with galactose side group). It is derived from the ground endosperm of Cyanopsis tetragonolobus, a plant of the leguminosae family. It has a straight chain of D-mannopyranose units joined by β (1-4) linkages with a side chain of D-galatopyronase joined to every other mannose unit by L (1-6) linkages. Xanthan gum on the other side, is a polysaccharide derived from the bacterial coat of Xanthomonas campestris.[6]

The fluctuation in colonic pH conditions and the nature of less fluid content in the colon may limit the expected drug release in the colon[7] The Eudragit are a family of polymers based on acrylic and methacrylic acids suitable for use in orally administered drug delivery systems.

These polymers are available in various grades possessing a range of physicochemical properties.[8]

Antiretroviral drugs are majorly used drugs for treatment of HIV infection. Zidovudine is a hydrophilic, antiretroviral drug with low oral bioavailability was used as a model drug. Zidovudine has low oral bioavailability (60%) thus necessitating frequent administration of large doses (200 mg every 4-6 h) to maintain therapeutic drug levels. Zidovudine shows dose dependent toxicity so to reduce side effect, dose should be reduce. To be able to reduce the number of administrations, it might thus be of interest to develop a controlled release preparation that provides lower but controlled drug concentration.[8-10]

The present research work was objected to formulate and characterize a colon-specific drug delivery system of zidovudine uing guar gum and xanthan gum as a polysaccharide and coated with Eudragit L100 and Eudragit S100 as coating polymers by the spray coating technique.

MATERIAL AND METHODS

Zidovudine was a kind gift from Ranbaxy Laboratories (Gurgaon, India).Guar gum, Xanthan gum Mapple Biotech Pvt. Ltd helped in the research by providing sodium starch glycolate in optimum amount. Instacoat solution (moisture seal) and Instacoat simply enteric were obtained through Ideal Cures Pvt. Ltd. Rest of the reagents were of analytical grade purchased from S.D Fine Pvt. Ltd.

Analysis of drug and preparation of calibration curve

Standard plots of Zidovudine were made by using series of standard solutions obtained by diluting the stock solution (100µg/ml) for calculation of the amount of drug present in dissolution samples at different time intervals and for confirmation of content uniformity. The calibration data and curves of zidovudine of different concentrations at pH 1.2, 6.8 and 7.4 buffer solutions. The values of regression coefficient resulted out to be 0.997, 0.999 and 0.999 at pH 1.2, 6.8 and 7.4 respectively. The obtained results were found to obey the Beer's law.

Preparation of core tablets

6 batches of formulations MF21- MF26 were prepared by using different polysaccharides (Guar gum, Xanthan gum) in varying concentrations and also with varying superdisintegrant

(sodium starch glycolate) concentration. To ensure the drug release only in large intestine, the prepared tablets were enteric coated by spray coating method using Eudragit L100 and S100 as enteric coating polymer. Tablets weighing 550 mg were prepared using minirotary tablet press (Fluidpack machinery) using 8 mm punch. Two types of punches were used, one flat punch and the other with the line of intersection for the preparation of 2 different shapes of tablets with same hardness of 4-5 kg/cm^2. Two different shaped tablets were prepared for easy distinction between tablets of different batches during and after coating. The formula of microbially triggered released tablets is as shown in table 1.

Coating of tablets

Before the enteric coating, seal coating is done to provide the moisture resistance property to the tablets. The seal coating is done with polymer solution (Instacoat-IC-MS-218) up to a weight gain of 3.5% w/w by using solvents isopropyl alcohol and methylene chloride in different ratio. After this, enteric coating of the tablets is done with coating solution (Instacoat-simply enteric) up to a weight gain of 35-40% w/w using solvent isopropyl alcohol. Enteric coated tablets are further coated with Instacoat Instaglow-001 to provide glow to the tablets. Another reason of seal coating is to protect the drug from any kind of interaction with the enteric polymer layer.

Formula for enteric coating of tablets is as shown in table 2 and 3**.**

Preformulation studies

FT-IR Analysis

FT-IR analysis of drug sample was performed to determine the purity of drug. A very large number of peaks were present in the FT-IR spectra of Zidovudine, out of which x peaks were found to be prominent in nature. Peaks of the obtained sample were compared with the peaks of pure drug as given in literature to authenticate the identity and purity of sample. Most of the peaks were found to be similar with the peaks mentioned in the literature.

Solubility

Drug sample was found to be freely soluble in Methanol, Ethanol, Isopropyl Alcohol and DMSO. Solubility of the sample was less when checked in water and acidic buffer of pH 1.2.

Melting Point

Melting point of the provided sample of drug was found to be 122-124^{0}C which was closer to the reported melting point value of 125^{0}C confirming the purity of the drug sample.

λ_{max} scanning of Zidovudine

The absorption maximum of drug solution was seen to be near 262.2 nm. Hence this test supported another identification test, proving the fact that the obtained sample is of pure Zidovudine as shown in Fig 1.

Evaluation Parameters[2,6]

Weight uniformity

Twenty tablets of each formulation were weighed individually and their average weight along with the standard deviation was calculated. Results for the weight uniformity were found to be within the range provided by the Indian pharmacopoeia.

Friability

Six tablets from each formulation were selected and weighed. The apparatus used was Roche Friabilator setting 25 rpm in which weighed tablets were placed for 4 minutes. The tablets were again weighed and were found to be within the limits provided by Indian pharmacopoeia (i.e. ± 1%).

Thickness

Thickness of tablets was determined by using Vernier calipers. Five tablets from each formulation were selected for determining thickness of both coated and uncoated tablets.

Content Uniformity

Content uniformity of ten tablets from each formulation was calculated by analysis of tablets. Ten tablets from each formulation were taken and crushed in a mortar pestle for calculation of drug content. To calculate content uniformity standard plot was utilized. From the results obtained, it was concluded that the formulation batches passed the test for content uniformity as they all contained active ingredient in a amount not less than the specified limit i.e. ± 15%.

Disintegration

The disintegration test was performed to check the intactness of coat in acidic medium and in phosphate buffer. Disintegration test was performed on 6 tablets of each formulation using Electrolab disintegration apparatus ED-2L (Mumbai). Initially tablets were tested in gastric pH (.1N HCl) for 2 hrs and then tested in simulated intestinal pH. From the results it was clearly seen that the coat remained intact in the acidic media preventing the drug release completely and gets dissolved in the phosphate buffer. Temperature was kept constant

throughout the study i.e. 37±0.5°c.

Scanning Electron Microscopy

Surface morphology of the enteric coated matrix tablets was studied through scanning electron microscopy (S-3400N) Hitachi Japan. Tablets were analyzed by scanning electron microscopy before and after dissolution, to see the changes in their surface and to predict the release mechanism. SEM was done by coating the samples with gold sputter in order to render them electrically conductive.

In vitro studies[2-4]

From the in vitro release rate data, one can predict that whether the dosage form will release the active ingredient in the required time period or not. In vitro dissolution studies or drug release studies were performed for microbially triggered zidovudine tablets using USP dissolution apparatus I (basket type, Electrolab tablet dissolution apparatus), at 50 rpm and 100 rpm at temperature 37 ± 0.5^{o}C, with dissolution medium of 900 ml. In order to simulate the pH change along the gastrointestinal tract, dissolution media of pH 1.2 and pH 7.4 were used sequentially referred to as sequential pH change method, followed by phosphate buffer of pH 6.8, simulating the environment of colon. Duration of the study was also varied depending upon the transit time of the corresponding organ. Firstly, dissolution was carried out in dissolution medium having pH of 1.2 for duration of 2 h (corresponding to the transit time of stomach). Afterwards, dissolution of the same formulation was continued in phosphate buffer pH 7.4 for 3 h (corresponding to the transit time of small intestine) followed by phosphate buffer pH 6.8 for 7 h (corresponding to the transit time of colon which generally varies from 10-30 h. Dissolution samples of the formulations were analyzed spectrophotometrically for determining the drug content and the percentage of drug released was calculated.

RESULT AND DISCUSSION

The granules prepared were evaluated for bulk density, tapped density, Hausner's ratio and angle of repose. The bulk density and tapped density of all the formulations was found to be in the range of 0.342-0.414 (gm/cm^3), 0.373-0.483 (gm/cm^3) respectively. The Hausner's ratio and angle of repose of all the formulations were in the range 1.09 to 1.17 and from 23.3 to 29.8 respectively indicating good flow properties. The tests of uniformity of weight, hardness, friability, thickness gave results which were within the official limits.

The enteric coating was done to the formulations to prevent their premature release in the gastric environment. The results showed it clearly that the coat remained intact for 2 hours in the acidic media preventing the drug release completely and get dissolved in the phosphate buffer at a time period of around 40 to 50 minutes.

In vitro studies were carried out to predict the release rate and amount of drug from the dosage form that reached into the body fluid. From the results obtained from in vitro study in 0.1N HCl, it was found that no drug was released into the dissolution medium clearly indicating the effectiveness of the enteric coat. This result was also in agreement with the disintegration test results and SEM of coated tablets.

In Vitro drug release at pH 6.8

The results of the study performed in the simulated colonic pH were plotted between cumulative % drug release v/s Time (min) which is mentioned in the table. The cumulative % drug release from the formulations in the initial hour of the study were found to be low even in the presence of superdisintegrant (sodium starch glycollate) due to the time taken by the polymers for transition from glassy to rubbery state and also the amount of superdisintegrant present. The higher the amount of superdisintegrant, higher the drug release from the formulation. After 4 hours of dissolution study, the cumulative % drug release was found to be 23.32% in MF 11, 31.28% in MF 12, and 29.27% in MF 21, 37.15% in MF 22 followed by 17.48% in MF 31, 25.15% in MF 32. The increase in drug release was noticed which can be explained by the fact that on rubbery transition of the polymer matrix, the seepage of dissolution fluid into the matrix tablets increases thereby causing greater drug dissolution and diffusion. The higher superdisintegrant amount in the formulation causes greater drug release because on contact with the dissolution fluid it swells and burst, creating pores and cavity in the tablets owing to faster release rate. After 7 hours of dissolution study, drug release was found to be 41.98% in MF 11, 55.21% in MF 12, and 49.65% in MF 21, 61.89% in MF 22 followed by 34.27% in MF 31, 43.87% in MF 32. Results of the in vitro dissolution study gave a clear indication that formulation MF 12 and MF 22 could be considered as optimized formulations for providing higher drug release as compared to other formulations as shown in table 4 and & Fig 2.

Effect of Polymers Combination and Concentration on Drug Release from Formulations Based on Microbially Triggered Approach

The data obtained from the in vitro studies proved that the drug release depends upon the

nature and concentration of polymer. Microbially triggered tablets were formulated using different combinations and concentrations of two natural hydrophilic polymers i.e. guar gum along with xanthan gum in the formulation. Formulations having lower percentage of xanthan gum showed higher drug release as compared to the formulations having higher percentage of xanthan gum because viscous gel formed with xanthan gum reduces the seepage of dissolution fluid into the core of tablets and leading to sustained drug release. Delay in drug release was also due to the immense swelling potential of xanthan gum which led to increase in diffusion path length. Dissolution results in pH 6.8 medium were also in correlation with above explanation as drug release was 41.98% in MF 11, 49.65% in MF 21 and 34.27% in MF 31 while it was 55.21% in MF 12, 61.89% in MF 22 and 43.87% in MF 32. Effect of polymer concentration can clearly be seen in above table 4 and Figure 3 (a) & (b).

Superdisintegrant Concentration affecting Drug Release from Formulations Based on Microbially Triggered Approach

Concentration of superdisintegrant in the formulation is a crucial factor for drug release. The higher the concentration of sodium strach glycolate, greater is the drug release from the matrix tablets. The cumulative % drug release shown by the formulation MF12 was higher than that of the MF11 despite the same concentration of polymer, due to the higher amount of superdisintegrant in MF12. In pH 6.8, the Cumulative % drug release in initial hour was 7.45% in MF 11 which increased to 24.36% in 4^{th} hour of dissolution followed by 41.98% at the end of dissolution study. Similarly MF 12 showed 11.52% of drug release in initial hour which increased to 30.58% after 4 hours and finally provided a total drug release of 55.21% at the end of dissolution study. Similarly MF22 and MF32 showed higher drug release than MF21 and MF31 respectively. The superdisintegrant amount affects the drug release due to the formation of pores and cavities, thereby allowing the easy seepage of the dissolution fluid into the tablet causing its swelling and burst effect. SEM of matrix tablets after dissolution testing in pH 6.8, proved the formation of pores and cavities. But because of the presence of hydrophilic rate controlling polymers, the drug showed sustained release pattern from the tablet matrix and preventing the rapid release of drug. Effect of superdisintegrant concentration can clearly be seen in Figure 4:(a),(b),(c)

In Vitro Drug Release Studies of Formulation MF 12& MF 22 in Presence of Rat Caecal Content

In case of microbially triggered formulations, the cumulative % drug release in three hours of dissolution testing in medium simulating intestinal conditions was found to be 8.12% in MF 12 and 12.54% in MF 22 as shown in (Table 4 and Figure 2). In dissolution medium of pH 6.8 with 4% rat caecal content MF 12 showed 12.02% of drug release in the initial hour of dissolution, which increased to 56.23% after 4 hours of dissolution and finally provided a drug release of 95.02% at the end of 7 hours of dissolution study in colonic environment. Similarly, formulation MF 22 showed 15.89% of drug release in the initial hour of dissolution, which increased to 54.23% after 4 hours of dissolution and finally provided a drug release of 95.45% at the end of 7 hours of dissolution study in colonic environment as showed in (Table4.1 and Figure 2.1). Although, formulations were differing in the concentration of polymers but the drug release from both the formulation was nearly similar. This was attributed to the reason that formulation MF 12 was having higher concentration of xanthan gum in the matrix of tablets as compared to MF 22. Due to presence of higher amount of xanthan gum in the formulation, more pronounced swelling of tablets was observed leading to increased exposed surface area to colonic microflora for degradation of guar gum. Rapid digestion of guar gum provided hastened drug release from the formulation. Presence of sodium starch glycollate (superdisintegrant) in higher amount was also contributing for the higher drug release. In case of MF 22, xanthan gum was present in lower amount leading to less swelling in the starting phase of dissolution but at later stages the drug release from tablets increased significantly due to the presence of sodium starch glycollate and digestion of guar gum by colonic microflora. Therefore, it was also clear from the result that although the drug release was faster in MF 22 but the effect of rat caecal content was more pronounced in case of MF 12. In both the formulations, presence of SSG in higher amount was the crucial factor for higher drug release by creating the pores and cracks in the matrix of tablets due to seepage of dissolution fluid as in table 5 & 6, Fig 5 & 6.

Model Fitting for Microbially Triggered Tablets

Dissolution data of all the formulations of microbially triggered tablets was fitted to zero order model, first order model, higuchi model and koresmeyer peppas model. From the results of the data fitting to four different models, the best linearity was shown by zero order models giving value of r^2 much closer to 1. So the order of drug release was said to follow zero order drug release kinetics. After predicting the order of drug release, mechanism of

drug release was determined by value of "n" which was equal to the value of slope given by the equation of line obtained by fitting the data to koresmeyer peppas model. Value of "n" was found to lie between 0.67 - 0.87 indicating anomalous behavior (also called as non-fickian diffusion) as a mechanism of drug release. This consists of phenomenon of diffusion and erosion of polymer matrix. This mechanism of drug release was also in agreement of presence of superdisintegrant in the formulations which causes tablets to degrade due to burst effect of superdisintegrant as shown in Figure 7 and table 7

Table 1: Formula for Colon Targeted Drug Delivery Using Microbially Triggered Approach

Ingredients	MF 11 (mg/tablet)	MF 12 (mg/tablet)	MF 21 (mg/tablet)	MF 22 (mg/tablet)	MF 31 (mg/tablet)	MF 32 (mg/tablet)
ZDV (Drug)	300	300	300	300	300	300
Guar gum + Xanthan gum (20% w/w) (Polymers)	55+55	Ratio (10 : 10) 55mg + 55 mg	Ratio (15 : 5) 82.5 mg + 27.5 mg	Ratio (15 : 5) 82.5 mg + 27.5 mg	Ratio (5 : 15) 27.5 mg + 82.5 mg	Ratio (5 : 15) 27.5 mg + 82.5 mg
Lactose monohydrate (Diluent)	94	92	94	92	94	92
PVP K30 (5 % w/v in propane-2-ol) (Binder)	27.5	27.5	27.5	27.5	27.5	27.5
Sodium starch glycollate (Superdisintegrant)	2	4	2	4	2	4
Talc (Glidant)	11	11	11	11	11	11
Magnesium stearate (Lubricant)	5.5	5.5	5.5	5.5	5.5	5.5

Table 2: Formula For Preparing Coating Solution Of Instacoat Simply Enteric

Ingredients	For 15 % w/w reconstitution level for solvent option I	For 10 % w/w reconstitution level for solvent option II
Instacoat (ISE-10001)	100 gm	100 gm
Isopropyl alcohol	425 gm (75%)	900 gm
Water	144 gm (25%)	Not Applicable
Total	669 gm	1000 gm

Table 3: Formula For Preparing Coating Solution of Instamoist shield

Solvent system	Reconstitutional level	Solvent option I	Solvent option II
Organic	5% w/w	Instamoistshield:40 gm	Instamoistshield:40 gm
		Isopropyl alcohol:266gm	Chloroform: 266 gm
		Methylene chloride:494 gm	Ethanol: 494 gm
		Total: 800 gm	Total: 800 gm

Table 4: Cumulative % Drug Release From Formulations In Dissolution Medium of pH 6.8

Time (min.)	Cumulative % drug released at pH 6.8					
	MF 11	MF 12	MF 21	MF 22	MF 31	MF 32
60	8.25	11.52	13.56	16.25	8.2	10.29
120	11.58	14.25	17.58	22.56	12.25	14.60
180	17.25	22.56	24.54	30.95	15.56	19.20
240	24.36	30.58	29.87	37.87	18.58	25.45
300	30.25	37.65	35.12	46.75	23.56	31.45
360	36.85	45.87	42.65	53.78	28.42	37.25
420	41.98	55.21	49.65	61.89	34.21	43.87

Table: 5. Cumulative % Drug Release from Formulation MF 12 & MF 22 In Dissolution Medium of pH 7.4

Time (min.)	Cumulative % drug release (pH 7.4)	
	MF 12	MF 22
60	0	0
120	6.02	8.89
180	8.12	12.54

Table: 6. Cumulative % Drug Released From Formulations MF 12 and MF 22 with Rat Caecal Content

Time (min.)	Cumulative % drug release (pH 6.8)	
	MF 12	MF 22
60	12.02	15.89
120	21.02	25.50
180	40.12	41.23
240	56.23	57.23
300	70.54	71.56
360	84.58	85.98
420	94.02	96.45

Table 7: Values of r^2, K and n Obtained From Different Kinetic Models Applied To Microbially Triggered Formulation

Formulation Batch code		Zero order kinetics	First order kinetics	Higuchi kinetics	Koresmeyer peppas kinetics
MF12	r^2	0.9928	0.9149	0.9658	0.7253
MF22	value	0.9964	0.8684	0.9634	0.6628

Fig 1: λ_{max} scanning of Zidovudine

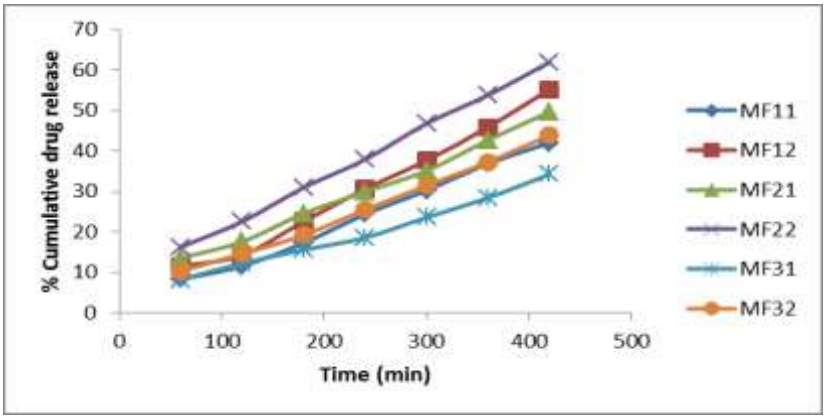
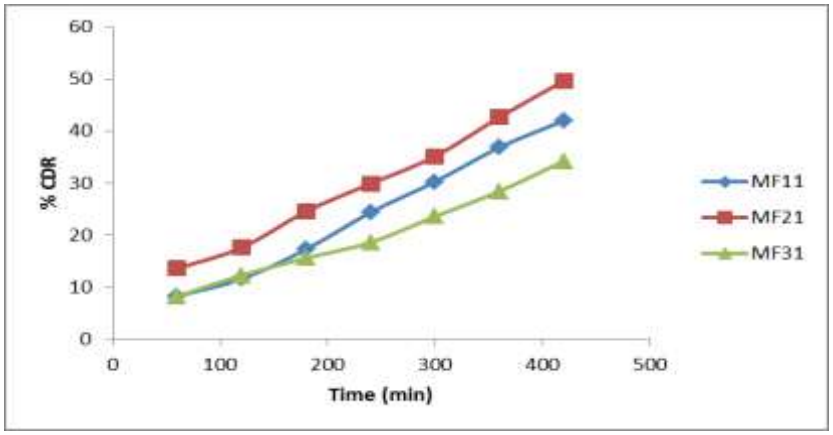
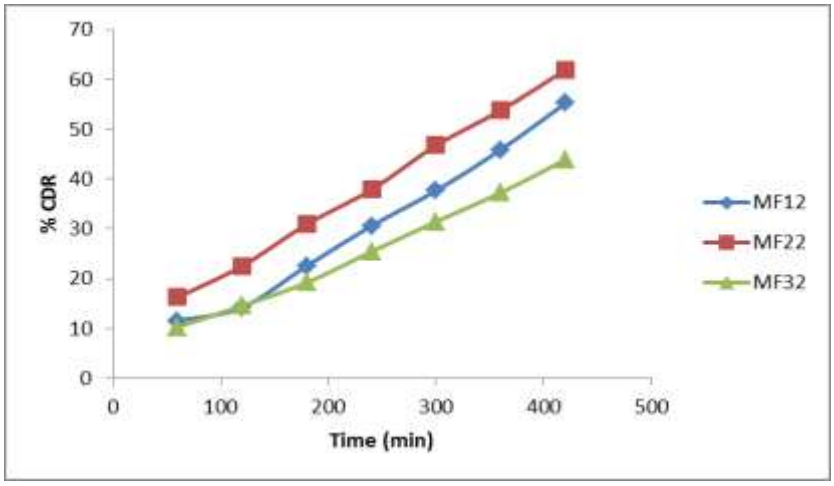


Figure 2 In vitro dissolution profile of microbially triggered tablets at pH 6.8



(a)



(b)

Figure 3 (a) & (b): Effect of polymer concentration on drug release

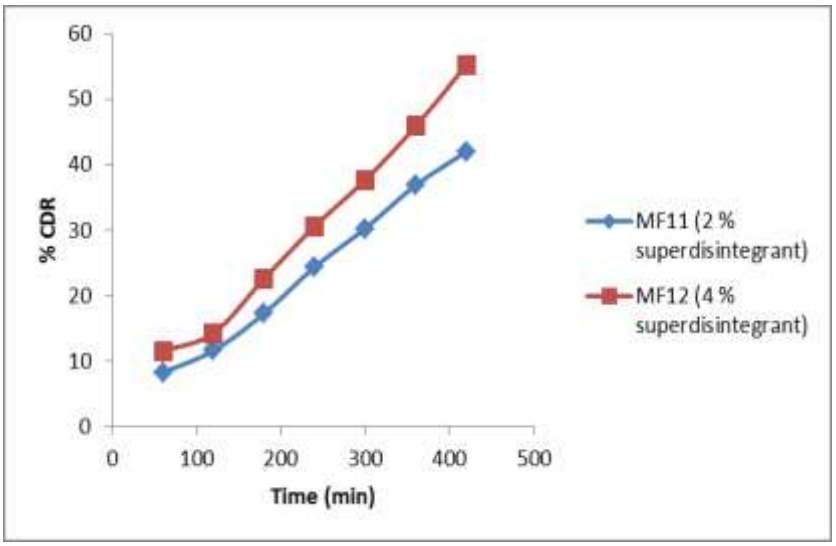


Figure (a)

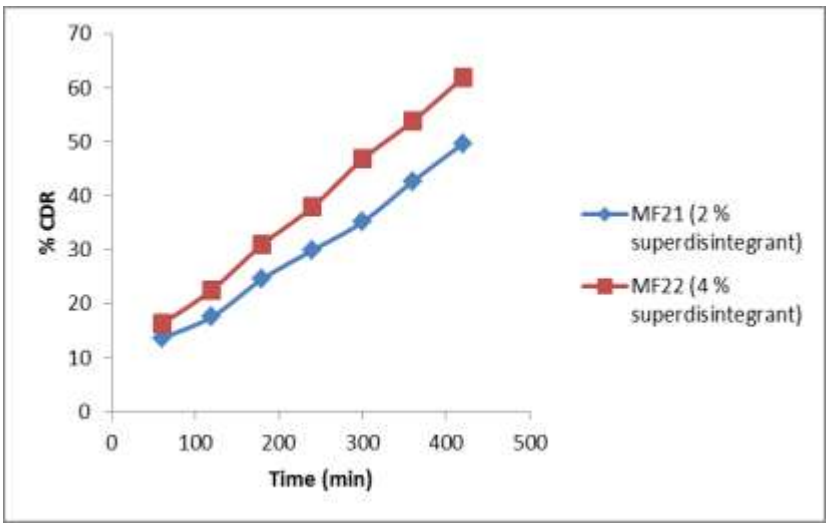
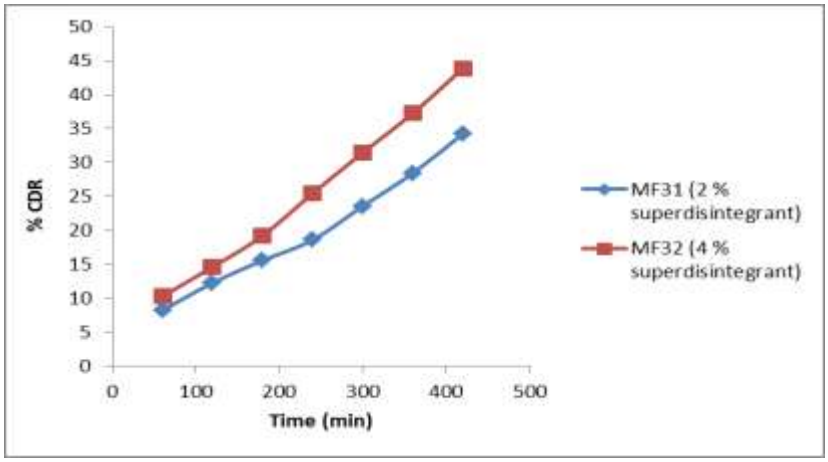


Figure (b)



(c)

Figure 4: (a) between F 11& F 12, (b) between MF 21 & MF 22, (c) between MF 31 & MF 32 indicating effect of sodium starch glycollate (superdisintegrant) concentration on drug release from tablets

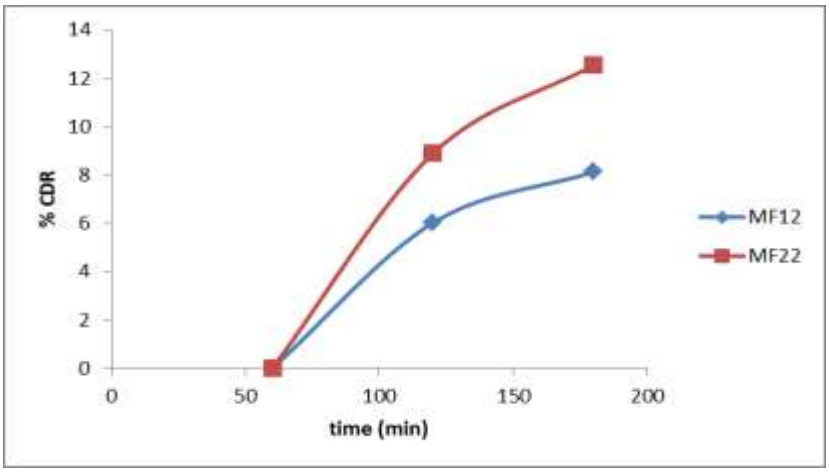


Figure 5: In Vitro Dissolution Profiles of Formulations MF 12 and MF 22 at pH 7.4

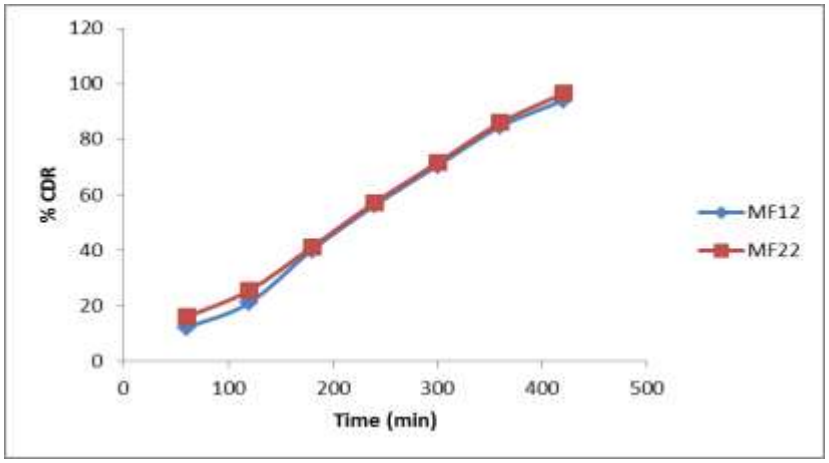
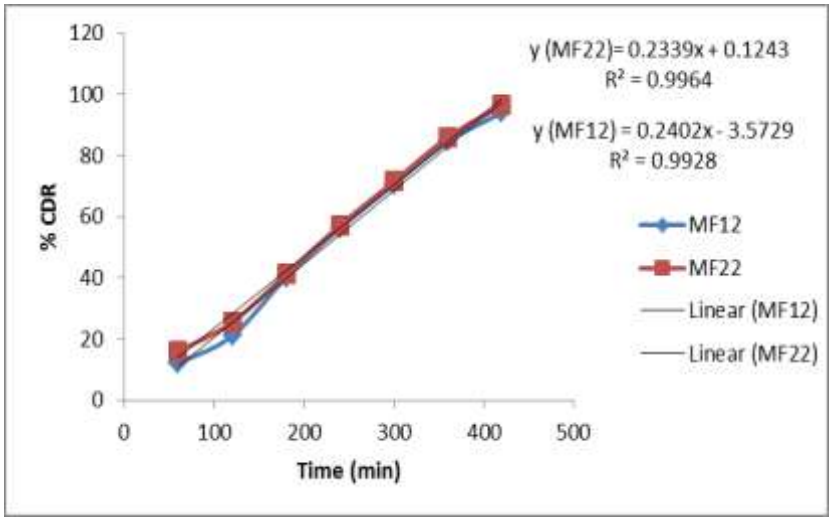
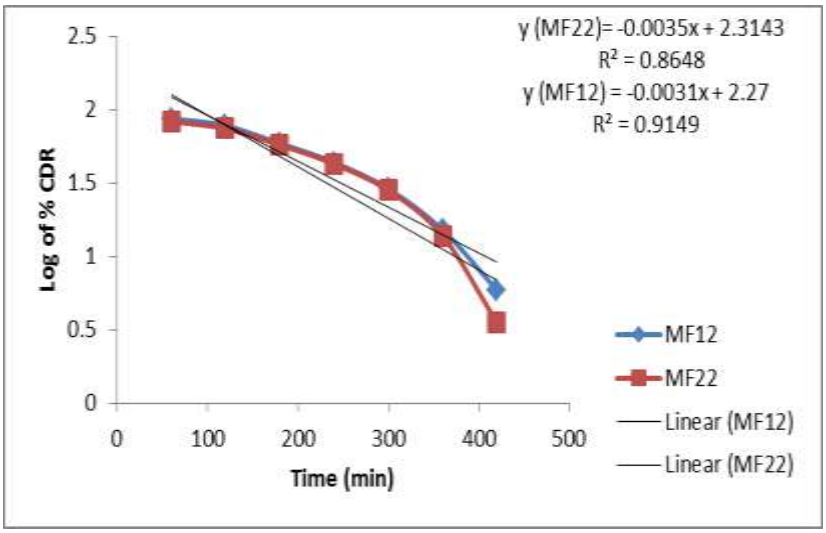


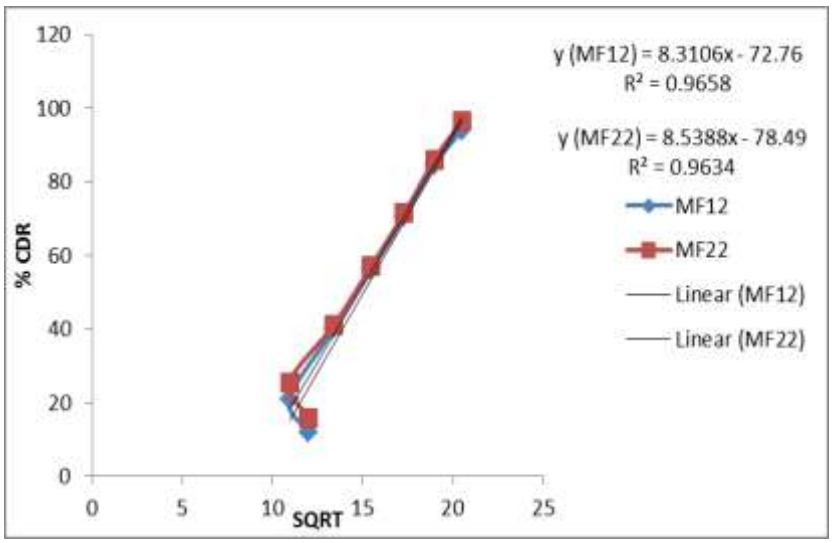
Figure 6: In vitro dissolution profiles of formulations MF 12 and MF 22 with rat caecal content



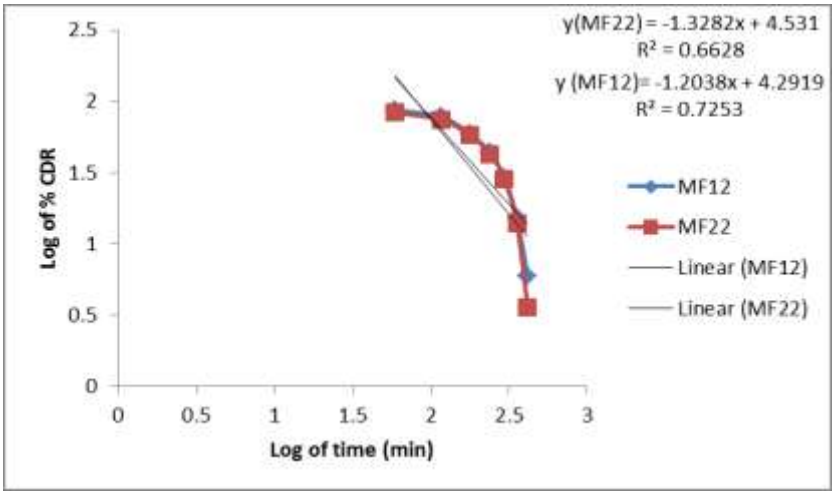
(a) Zero order



(b) First order



(c) Higuchi Model



(d) Koresmeyer

Fig 7: various kinetic models (a) Zero order (b) First order (c) Higuchi model (d) Koresmeyer Peppas

CONCLUSION

The enteric coated polysaccharide matrix tablets of Zidovudine based on microbially triggered approach was successfully prepared. From the results of present study, it was concluded that the combination of polymers guar gum and xanthan gum showed best release characteristics in formulations. Simultaneously, concentration of superdisintegrant (used as 2.0%) also affected the drug release as higher the concentration of superdisintegrant i.e. sodium starch glycolate, faster is the drug release from matrix system. Coating has successfully sustained release of zidovudine in buffers at pH 1.2 and 7.4, while providing potential for efficient release of zidovudine at pH 6.8. Drug release kinetics of this system best corresponds to first order and the mechanism of drug release was corresponding to anomalous behavior (combination of diffusion and erosion) as calculated from “n” value obtained from koresmeyer peppas model.

AKNOWLEDGEMENT

We are having sincere thanks to Dean & Director, University Institute of pharmaceutical Sciences, Kurukshetra University, Kurukshetra for providing us all the requisite chemicals and instruments to be used for our research work.

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