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Research Article

EFFECT OF HYDROPHOBIC EXCIPIENTS ON RELEASE KINETICS OF CIPROFLOXACIN FROM KOLLIDON® SR EMBEDDED MATRIX TABLETS

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Abstract

Controlled release (CR) Ciprofloxacin (CFX) matrix tablets were prepared using Kollidon® SR as a matrix former and different hydrophobic excipients as release modifier. Six hydrophobic excipients: glyceryl monostearate, glyceryl palmitostearate, glyceryl dibehenate, cetyl alcohol, stearic acid and bees wax were used at 10% and 20% level in the matrix systems. Prepared tablets showed good tabletting properties. *In vitro* dissolution study was carried out in 0.01 N HCl solutions for 10 hours. Matrix systems consisting of 20% of the hydrophobic excipients showed more release retarding capacity than those consisting of 10% level of the excipients. In case of 20% level of the excipients, ciprofloxacin release was 64% for glyceryl monostearate, 60% for glyceryl palmitostearate, 68% for glyceryl dibehenate, 52% for cetyl alcohol, 74% for stearic acid and 94% for bees wax. Drug release from the matrix systems followed non-fickian or anomalous mechanism.

Key Words: Ciprofloxacin, Kollidon® SR, Sustained release, Matrix tablet, Hydrophobic excipient

INTRODUCTION

Many strategies are available for the design and development of modified-release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration, and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range.[1]

Ciprofloxacin (CFX) is a fluoroquinolone derivative with outstanding antibacterial activity against gram-negative and some gram-positive bacteria as well as on some Chlamydia and Mycoplasma, and many mycobacterium species.[2,3,4] Its action takes place via the inhibition of the bacterial DNA gyrase which is an essential enzyme for DNA replication and synthesis. In animals, quinolones, especially CFX, exhibit favorable pharmacokinetic properties, their apparent volume of distribution suggested substantial tissue penetration.[5,6] However, to ensure optimum level of CFX in blood for a longer period of time, it is always desire to administer sustained release dosage forms of CFX and for the same purpose, different experiments, in the past, were carried out to design and characterize sustained release CFX tablets[7,8]

For the same purpose, sustained release matrix tablets of CFX were prepared using Kolidon® SR where glyceryl monostearate, glyceryl palmitostearate, glyceryl dibehenate, cetyl alcohol, stearic acid and bees wax were used as hydrophobic excipients.

EXPERIMENTAL DETAILS

Materials

Ciprofloxacin betaine was purchased from Organo-Chem Pvt. Ltd. India. Kollidon® SR (BASF, Germany), glyceryl monostearate (e.g. Danisco, UK), glyceryl palmitostearate (e.g. Precirol®, Gattefosse France), glyceryl dibehenate (e.g. Compritol AT088®, Gattefosse France), cetyl alcohol (BDH Chemicals Ltd., England), stearic acid (BDH Chemicals Ltd., England), bees wax (Koster Keunen Inc. USA), talc (Whittaker, Clark and Daniels Inc, USA), Aerosil 200 (Degussa, Germany), magnesium stearate (Wilfrid Smith Ltd, UK) were used as gift.

Preparation of matrix tablets of ciprofloxacin betaine

Kollidon® SR embedded matrix tablets of CFX were prepared using different hydrophobic excipients at 10% and 20% (wt/wt) level (see table 1 & 2) by direct compression method. CFX tablets of different compositions were compressed by a Perkin- Elmer laboratory hydraulic press equipped with a 13 mm flat faced punch and die set. Compression pressure and time were 5 ton and 1 minute respectively. Prepared tablets were then preserved in a desiccator for further experiments.

Physical characterization of designed tablets

The drug content of the manufactured tablets of each batch was determined in duplicate. For each batch, 10 tablets were taken, weighed, and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in 0.01 N hydrochloric acid solution and analyzed after making appropriate dilutions. The weight variation was determined by taking 10 tablets using an electronic balance (AY 120, Shimadzu Corp., Japan). Tablet thickness, diameter, and hardness were determined for 6 tablets using a DR. SCHLEUNIGER PHARMATRON Tablet Tester 8M (UK). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm.

In vitro release study of ciprofloxacin from designed tablets

Release rate for all the designed formulations was studied up to 10 hours using a USP tablet dissolution tester (Dissolution Tester TDT-08L, Electrolab, Mumbai, India), type 2 (paddle method), in 900 mL of 0.01 N hydrochloric acid solution at 37.5 ± 0.5°C. The stirring speed was set at 50 rpm. At predetermined time intervals, a 10 mL sample was withdrawn and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed. Cumulative percentage of the drug released was calculated, and the mean of 6 tablets was used in data analysis.

RESULTS AND DISCUSSIONS

Physical properties of the designed tablets

The physical appearance, tablet thickness, diameter, hardness, friability, and weight variation of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 3. Except the hardness values, other tabletting properties of the prepared tablets for both 10% and 20% level of the hydrophobic excipients were within the same range. For 10% level of the excipients, maximum hardness value was found 223 newton for glyceryl palmitostearate (GPS). While 20% excipients were used, tablets prepared using both bees wax and GPS showed maximum hardness values.

In vitro release of ciprofloxacin

Figure 1 and Figure 2 show the cumulative percent of CFX released versus time for matrix-embedded SR tablets of CFX. Figure 1A shows

the release of CFX from matrices containing 10% wax-lipid load (i.e.50 mg hydrophobic material). At this wax-lipid concentration, glyceryl palmitostearate (GPS) imparted the strongest retarding effect on CFX. About 71% of CFX was released after 10 hours of dissolution period with an initial release of 25 % after 1 hour. The release was almost linear throughout the dissolution period. GPS is a water insoluble excipient which is used as tablet and capsule lubricant. It is a mixture of mono-, di-, and tri-, glycerides of C_{16} and C_{18} fatty acids.[9] Due to this lipophilic nature of the GPS, it has been used as a matrix former in sustained release dosage forms.[10]

Table 1: Formulation of Ciprofloxacin-Kollidon® SR Matrix Tablets with 10% Excipients.

MATERIALS (mg)	CKM1	CKP1	CKD1	CKCA1	CKS1	CKB1
Ciprofloxacin Betaine	250	250	250	250	250	250
Kollidon® SR	200	200	200	200	200	200
Glyceryl Mono Steartate	50					
Glyceryl Palmitosteartate		50				
Glyceryl Di Behenate			50			
Cetyl Alcohol				50		
Stearic Acid					50	
Bees Wax						50

*** Each formula also contains 1 mg of each of aerosil 200, magnesium stearate, and talc.**

Table 2: Formulation of Ciprofloxacin-Kollidon® SR Matrix Tablets with 20% Excipients

MATERIALS (mg)	CKM2	CKP2	CKD1	CKCA1	CKS1	CKB1
Ciprofloxacin Betaine	250	250	250	250	250	250
Kollidon® SR	150	150	150	150	150	150
Glyceryl Mono Steartate	100					
Glyceryl Palmitosteartate		100				
Glyceryl Di Behenate			100			
Cetyl Alcohol				100		
Stearic Acid					100	
Bees Wax						100

*** Each formula also contains 1 mg of each of aerosil 200, magnesium stearate, and talc.**

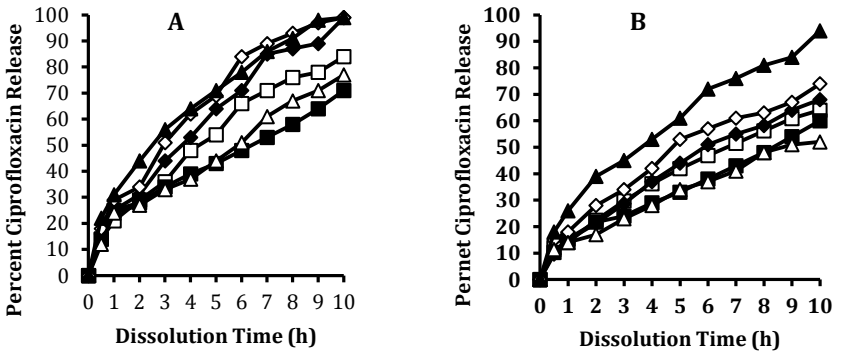

Figure 1: Zero order release of ciprofloxacin from Kollidon SR embedded matrix tablet containing (A) 10% of escipients and (B) 20% of excipients where (□) = glyceryl mono-stearate, (♦) = glyceryl dibehynate, (■) = glyceryl palmitostearate, (◊) = stearic acid, (▲) = cetyl alcohol, (Δ) = bees wax.

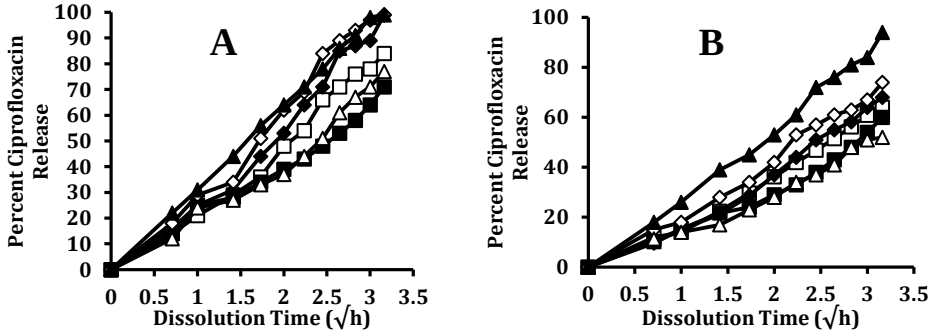

Figure 2: Higuch release model of ciprofloxacin from Kollidon SR embedded matrix tablet containing (A) 10% of escipients and (B) 20% of excipients where (□) = glyceryl mono-stearate, (♦) = glyceryl dibehynate, (■) = glyceryl palmitostearate, (◊) = stearic acid, (▲) = cetyl alcohol, (Δ) = bees wax.

Glyceryl dibehenate (GB), on the other hand, is a mixture of glycerides of fatty acids, mainly behenic acid and is also practically insoluble in water.[9] This lipophilic nature of the excipient also caused CFX to be released from the matrix for up to 10 hours of dissolution. After 10 hours, 99.1% CFX was released from the matrix system. GB is a tablet and capsule lubricant.[11] But most importantly,

GB has a good release retarding capacity which played the major role in controlling the release of CFX from Kollidon® SR embedded matrix tablet.[12,13,14] Similar but more pronounced reduced release was observed while glyceryl monostearate (GMS) was incorporated in the matrix formulation. Percent release of CFX was 84.15±4.014% for this batch. GMS is a lipophilic emulsifying agent (HLB 3.8) which is practically insoluble in water.[9] Besides, it is a lubricant for tablet manufacturing and may be used to form sustained release matrices for solid dosage forms.[15]

CFX release from stearic acid (SA) matrix was rapid, almost a zig-zag release curve was found where almost 100% CFX was released after 10 hours of dissolution. The free carboxylic acid group (-COOH) present in stearic acid enhanced the formation of hydrogen bonding with surrounding dissolution medium and facilitated wetting of matrix and consequent higher release of CFX. Cetyl alcohol (CA), because of their lower hydrophilic characteristics than polymers containing carboxylic acid moiety, released lesser amount of drug (77.2% CFX after 10 hours). Again, the molecular length and cross-sectional area for stearic acid is 25 A° and 22 A° respectively which is higher than those of cetyl alcohol (22 A° and 21 A° respectively). This higher molecular dimension of stearic acid also contributed to enhanced formation of hydrogen bond and elevated extent of CFX release.[16] It can be noted that, at 10% level, waxes and hydrophobic materials used are not efficient enough in sustaining the release of drug.

Bees wax (BW), consisting of 70-75% of a mixture of various esters from C_{26}-C_{32} alcohols, particularly palmitic, hydroxypalmitic, d-β-dehydropalmitic and cerotic acid, could not impart any sustaining effect on CFX release.[9] Total amount of CFX in the matrix system was virtually released within the first hour of dissolution from bees wax matrix. It was 31% of CFX which was maximum among the all within the first hour.

The release profile of CFX from different matrix-forming agents of this class indicates the existence of a close initial rapid release was observed with all the polymers that clearly necessitate the increment of matrix-retarding agents and/or incorporation of rate-modifiers to get a desirable release profile. Increasing the wax-lipid level markedly decreased the rate and extent of drug release as can be observed from figure 1B where 20% of the hydrophobic excipients were used (i.e. 100 mg). In this case, highest amount of CFX was released from bees wax matrix system (i.e. 89%) with initial release of 26% within first 1 hour. Release profile of CFX from GPS and CA was almost super-imposable on each other. The cumulative release after 10 hours was 60.01% and 52.11% respectively for these two matrices. As can be observed from the figure,

64.21%, 68.01%, and 74.0% of CFX was released from GMS, GB and SA matrices respectively. Except for bees wax matrix, increasing the wax-lipid level greatly reduced the initial release. The fact can be reasoned in the way that, an increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug).[17] Increment in polymer content also increases the tortuosity of the matrix and drug diffusion path-length which in turn slows down diffusion and erosion from/of the matrix.[18]

Kinetic approach of drug release from wax matrices

The mechanism of drug release from wax matrices has been a matter of controversy since wax systems tend to be crude and more heterogeneous than polymeric systems.[19] It has been suggested that the mechanism of release from wax matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of drug through the matrix being insignificant.[20,21] Others have reported that release from a typical wax matrix is diffusion-controlled and is best described by Higuchi's $t_{1/2}$ model.[22,23,24,25] In our study, different kinetic equations (Zero-order and Higuchi's equation) were applied to interpret the release rate from matrix system. The best fit with higher correlation was found with the well-known Higuchi equation, Eq. (1)

$$Q = 2C_0 (Dt/3.14)^{½} \text{ .....(1)}$$

Where Q is the amount of the drug released per unit area (cm^2), C_0 is the initial quantity of the drug (mg), D is the diffusion co-efficient and t is the time after application. As C_0 and D are essentially constant, the equation can be reduced to Eq (2)

$$Q=K't^{1/2} \text{ ... ...(2)}$$

Where K′ is the constant or the Higuchi release rate constant. The data, when treated with this above equation by plotting the percent of CFX release (Q) against the square root of time ($t_{1/2}$), yielded a fairly good linearity confirming that the release permeation data followed the Higuchi model (R2 > 0.98). This was true for all the formulations irrespective of excipient type and loading (Figure 2).

After liberation of the surface drug, the release of CFX became extremely slow and steady as the hydrophobic polymers started impeding wetting and subsequent penetration of dissolution medium into the matrix. For 20% wax-lipid loading, extrapolation of the linear portion of the Higuchi plot again showed a negative value on the time axis indicating the presence of burst release. However, the extent of burst release was much lower than those found with 10% wax-matrix concentration. At this level, hydrophobic materials exerted potential repulsion of solvent-front from the matrix surface. Again, reduction of Kollidon® SR also hindered the pore formation and disintegration process within the matrix. It should be mentioned that, the initial burst release of the drug from the hydrophobic system is often therapeutically undesirable because the total amount of drug released is remarkably influenced by this initial control of release from the dosage form.[26] The presence of burst release for all the polymers being studied clearly indicates that hydrophobic materials at 10% level were not sufficient to produce a desirable pharmacokinetic profile. However, at 20% wax-lipid content, burst release can sufficiently be minimized and a provision to control CFX release in a well-defined pattern can be explored as can be observed from Figure 2B. The Higuchi release rate (%release.$h^{-1/2}$) was calculated from the slope of higuchi release curves. At 10% wax-lipid level, the Higuchi Release rate (%release.$h^{-1/2}$) was the highest with SA and GD matrix which were 33.94 and 32.4 respectively (Figure 3A). The release rate was 28, 20.91, 24.12 and 32.25 for GMS, GPS, CA and BW respectively.

The Higuchi release rate was found to decrease considerably with increment of wax-lipid concentration. SA and GD were found to release CFX at the rate of 23.74 and 22.66 %/$hour^{1/2}$ respectively at this fat-wax level. However, beeswax, at 20% w/w of the matrix, released CFX at a faster rate than any other hydrophobic materials (29.47%/$hour^{-1/2}$). GMS, GPS and CA showed the higuchi release rate of 20.99, 18.08 and 16.84 %/$hour^{-1/2}$ respectively. The effect of different wax-lipid based matrix systems on Higuchi release rate can be placed in the descending order of: SA> GD> BW> GMS > CA> GPS. Two factors, however, diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential Eq. (1), which is often used to describe the drug release behavior from polymeric systems:

$$M_t/M_\alpha = Kt^n \text{ ... ... (3)}$$

Where Mt/Mα is the fractional (0.1-0.7) 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 depends on and 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 (Zero order) release and >0.89 for super case II type of release.[27] Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain and anomalous transport (Non Fickian) refers to the summation of both diffusion and dissolution controlled drug release. From the above equation the n and K values for different formulations have been calculated to identify the drug release mechanism. Akbuga[28] applied this equation to evaluate the drug release mechanism from chitosonim maleate matrix tablets while Fickian release and / or case II release is presumed to contribute to drug release from wax matrix granules as reported by Sato *et al*.[29] These investigations clearly rationalize the

application of bi-exponential equation to wax-matrix tablets. In Table 4, the values of n, and the correlation co-efficient (R^2) obtained with wax-lipid matrix tablets are summarized. The value of correlation coefficients R^2 (>0.98) are high enough to evaluate CFX dissolution behaviour from wax matrix by Eq. (3). The table shows that, at 10% polymeric level, GMS, GD, GPS, SA, CA and BW demonstrated the tendency of drug release by non-fickian or anomalous mechanism observed from their n values. This suggests that, at this excipient load, both diffusion and dissolution controlled CFX release mechanism was predominant and this type of mechanism was also proved according to the R^2 values of the release curves. R^2 values of the curves were > 0.96 for both zero order and higuchi model. At 20% level, all the hydrophobic materials being studied showed a clear trend to release drug by non-fickian or anomalous mechanism.

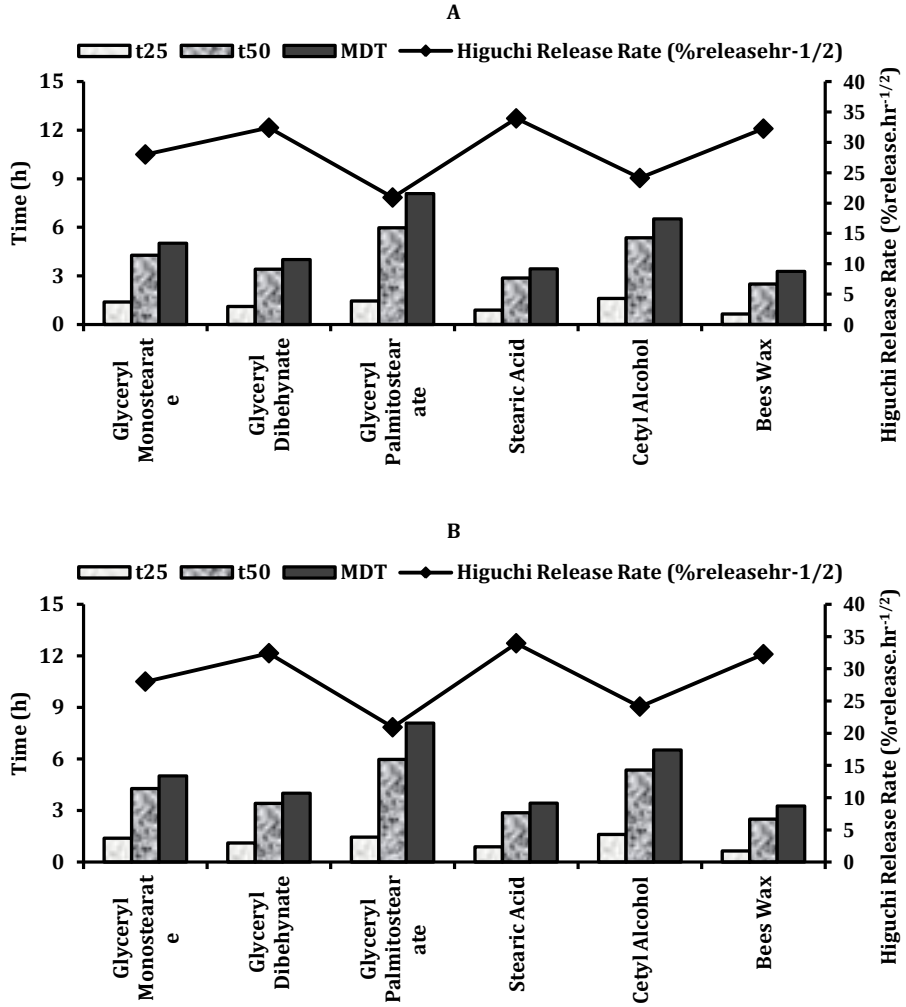

Figure 3: Time for 25% release (t_{25}), 50% release, mean dissolution time (MDT) and higuchi release rate of Ciprofloxacin from different matrix systems composed of 10% (A) and 20% (B) hydrophobic excipients.

Table 3: Physical properties of the matrix tablets prepared using 10% and 20% level of hydrophobic excipients

Batch	Weight Variation¥	Thickness (mm)Ψ	Diameter (mm)*	Hardness (newton) §	Friability
	at 10% level of the excipients				
Glyceryl Monostearate	± 1.2	3.4	12.65	187	< 0.5
Glyceryl Dibehenate	± 1.5	3.3	12.54	189	< 0.5
Glyceryl Palmitostearate	± 1.1	3.2	12.38	223	< 0.5
Stearic Acid	± 1.1	3.3	12.34	195	< 0.5
Cetyl Alcohol	± 1.3	3.5	12.39	212	< 0.5
Bees Wax	± 1.3	3.2	12.44	201	< 0.5
	at 20% level of the excipients				
Glyceryl Monostearate	± 1.1	3.5	12.31	212	< 0.5
Glyceryl Dibehenate	± 1.1	3.6	12.37	221	< 0.5
Glyceryl Palmitostearate	± 1.4	3.5	12.41	231	< 0.5
Stearic Acid	± 1.0	3.7	12.52	217	< 0.5
Cetyl Alcohol	± 1.3	3.4	12.61	204	< 0.5
Bees Wax	± 1.1	3.5	12.38	228	< 0.5

¥ Weight variation ± standard deviation (SD) from mean values (n=10)
Ψ Mean thickness of tablets ± SD (n=6).
*** Mean diameter of tablets ± SD (n=6).**

§ Mean hardness of tablets ± SD (n=6).

Table 4: Kinetic Parameters of Matrix Systems

Hydrophobic Excipients	10% Level				20% level		
	Zero	Higuchi	n		Zero	Higuchi	n
Glyceryl Monostearate	0.964	0.983	0.61	Glyceryl Monostearate	0.964	0.983	0.61
Glyceryl Dibehenate	0.967	0.98	0.61	Glyceryl Dibehenate	0.967	0.98	0.61
Glyceryl Palmitostearate	0.948	0.982	0.48	Glyceryl Palmitostearate	0.948	0.982	0.48
Stearic Acid	0.941	0.985	0.59	Stearic Acid	0.941	0.985	0.59
Cetyl Alcohol	0.971	0.968	0.57	Cetyl Alcohol	0.971	0.968	0.57
Bees Wax	0.93	0.998	0.51	Bees Wax	0.93	0.998	0.51

CONCLUSION

In case of both 10% level and 20% level of hydrophobic excipients, matrix tablets of ciprofloxacin prepared using Kollidon® SR showed good controlled release property. Especially, bees wax and glyceryl palmitostearate (at 20% level) containing matrix systems released only 52% and 60% of ciprofloxacin after 10 hours. Thus these matrix systems might be considered to release the water soluble drugs like ciprofloxacin for more than 10 hours.

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