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DESIGN AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LEVOFLOXACIN EMPLOYING ALMOND GUM

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ABSTRACT

In the present investigation, studies were undertaken on the design of sustained release matrix tablet of a widely useddrug levofloxacin hemi hydrate. Matrix tablets of levofloxacin hemi hydrate were prepared by employing both hydrophilic and hydrophobic polymers (HPMC, Ethyl cellulose, Compritol and almond gum). The tablets prepared by employing the relatively unexplored hydrophilic almond gum showed acceptable pharmaceutical properties. Matrix tablets prepared with polymers other than almond gum though gave a slow release. It was observed that more than 90% of drug was released by 8 hrs. A slow drug release of about 90% extended upto 12 hrs was obtained with tablets prepared by employing almond gum. Studies are also made on the influence of changing the microenvironment of the matrix on the release profile of the drug. Inclusion of citric acid in the formulation favored the release of the drug from the matrix tablets.

Key words: Levofloxacin, Sustained release, Compritol, Almond gum, Microenvironment.

INTRODUCTION

Sustained-release dosage forms reduce side effects and increases safety and patient compliance by reducing the frequency of dosing[1]. Drug release-retarding materials play an important role in such systems. Various materials are thus investigated for sustaining the release from the drug-loaded matrices. Some of them such as a chitosan, sodium alginate and xanthan gum have been thoroughly reviewed[2,3] earlier. Of the various approaches to formulate sustained release matrices, one method is to incorporate drug within the release retarding polymer. Most commonly used polymers for such operations are cellulose ether derivatives, including hydroxypropyl methylcellulose (HPMC)[4,5]. Due to nontoxicity, easy

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handling and no requirement of specified technology for production of sustained-release tablets, HPMC is often used as release-retarding material. However there is a search for new and more efficient polymers for preparing the sustained release matrix tablets. Designing a matrix tablet for a water soluble drug is always highly challenging. This is because the highly soluble drug rapidly diffuses out of the matrix. Various approaches are employed to overcome this difficulty. One such is employing a combination of hydrophobic and hydrophilic matrices. In the present investigation, a relatively water soluble drug such as levofloxacin is taken as a model drug. While levofloxacin exhibits higher solubility in the acidic gastric fluids – in the alkaline intestinal fluids it is less soluble. So the release profile of the drug from matrix tablets which traverse across-gastric and intestinal is likely to be different and complicated. So in the present work, the effect of dispersing the drug in a lipophilic retardant such as compritol and then entrapping the dispersion in a combination of hydrophilic and hydrophobic polymers is investigated. The utility of a relatively unexplored hydrophilic gum-almond gum is also explored to comparatively evaluate such matrix tablets prepared with that of tablets prepared using combined hydrophilic and hydrophobic polymers. The influence of the presence of citric acid in the matrix tablet on the release of the drug was also evaluated. Levofloxacin hemihydrate is used as antimicrobial agent for the treatment of a variety of infectious diseases[6,7]. Levofloxacin has a biological half- life of 5-7 hours[8] and administration of levofloxacin in sustained release dosage forms offers the advantage of reduced frequency of administration and prolonged plasma concentration improving the efficacy of the drug.

EXPERIMENTAL

Materials

Levofloxacin hemihydrate (gift sample from Dr. Reddy Laboratories), compritol, ethyl cellulose, hydroxy propyl methyl cellulose (HPMC) are purchased from s.d. Fine Chemicals, India, Lactose, citric acid are procured from Loba Chem, India, Almond gum was procured from Girijan Corporation, Visakhapatnam. All other chemicals are of analytical grade.

Preparation of matrix tablets

From our initial studies, it was observed that matrix tablets of levofloxacin hemi hydrate employing hydrophilic polymers and hydrophobic polymers like HPMC and ethyl cellulose could not properly sustain the drug release for prolonged period. So in our further attempts for prolonging the drug release a modified approach as given below is employed.

The tablets (batch size of 100 tablets) were prepared as per the formula given in Table 1. Initially compritol was taken in a porcelain dish and kept on hot plat. The

temperature was adjusted to 70°C. In the molten mass, the drug levofloxacin hemi hydrate was dispersed. The mixture was allowed to cool and solidify at room temperature. The solidified mass was pulverized in mortar and sieved through a 100# screen. The drug dispersed in the molten matrix was now blended with other accurately weighed ingredients as shown in Table 1. Talc and magnesium stearate were now added and blended uniformly and then the powder blend is compressed directly by employing 10 mm diameter flat punches using a rotary 16 station tablet punching machine.

Table 1: Details of matrix formulations prepared*

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Levofloxacin hemi hydrate	250	250	250	250	250	250	250	250	250
2	Compritol	50	100	150	-	-	-	-	-	-
3	Ethyl cellulose	25	50	75	-	-	-	-	-	-
4	HPMC (5 CPS)	25	50	75	25	50	75	50	50	50
5	Almond gum	-	-	-	50	100	150	100	100	100
6	Lactose	240	140	40	265	190	115	165	140	115
7	Citric acid	-	-	-	-	-	-	25	50	75
8	Talc	5	5	5	5	5	5	5	5	5
9	Magnesium stearate	5	5	5	5	5	5	5	5	5

*Formulations F1 to F3 – Set 1; Formulations F4 to F 6 – Set II; Formulations F7 to F9 – Set III

Characterization of matrix tablets

The flow properties of the powder blends of the formulations shown in Table 1 are first evaluated. The Carr Index, Hausner Ratio and the Angle of Repose are determined and the data is shown in Table 2.

Table 2: Details of flow characteristics of matrix formulations before compression

Formulation	Carr index	Hausner ratio	Angle of repose
F1	28.11	1.68	29.34
F2	31.25	1.60	34.56
F3	35.87	1.59	37.12

Cont…

Formulation	Carr index	Hausner ratio	Angle of repose
F4	21.05	1.21	19.66
F5	20.09	1.25	21.22
F6	19.05	1.29	18.34

Drug content

10 Tablets of containing the equivalent of 250 mg of levofloxacin hemi hydrate were collected randomly, powdered and shaken with 60 mL of distilled water for 1 hour. The resulting solution was diluted to 100 mL and then filtered. The filtrate was suitably diluted and analyzed for levofloxacin hemi hydrate by measuring the absorbance at 293 nm.

Hardness

Hardness of the tablets was determined by using Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turningthe threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial reading from the final reading.

Weight variation

20 tablets were collected at random and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using formula.

Percent weight variation = [(Average weight – Individual weight)/Average weight] × 100

Friability

The Roche Friability Test Apparatus was used to determine the friability of the tablets. 10 tablets were selected, de-dusted and weighed. Then they were placed in a drum and rotated for 100 times in a period of 4 mins. Then the tablets were de-dusted and were reweighed. The percent friability was calculated by the formula.

Percent friability = [(Initial weight – Final weight)/Initial weight] × 100

The results of hardness, weight variation and friability were given in Table 3.

Table 3: Hardness, friability and weight variation of different formulations of matrix tablets

Formulation	Hardness Kg/cm^2	Friability (%)	Weight variation (mg)
F1	3.71	0.87 ± 0.07	601 ± 2.27
F2	4.12	0.69 ± 0.18	599 ± 2.36
F3	3.87	0.81 ± 0.14	599 ± 3.47
F4	5.81	0.19 ± 0.06	601 ± 0.78
F5	6.05	0.16 ± 0.16	600 ± 1.06
F6	6.12	0.14 ± 0.26	601 ± 1.16

Drug release study

Drug release study from the matrix tablets was studied in 0.1 N hydrochloric acid forthe first 2 hrs and in phosphate buffer of pH 7.2 for remaining 10 hrs by employing USP XXIV Type I dissolution test apparatus (Lab India model). A speed of 50 rpm and a temperature of 37^{o}C and volume of 900 mL of dissolution medium were employed in each study. 5 mL samples were withdrawn using 0.45 micron filter at various time intervals and the same volume of the medium is replaced by fresh medium. Samples were assayed for Levofloxacin by measuring the absorbance at 293 nm by employing ELICO (Model SL 164) double beam UV spectrophotometer. The results of the release studies shown in Fig. 1 to 3 and given in Table 4.

Table 4: Correlation coefficient and release exponent values for different kinetic models

S. No.	Formulation	Zero order	First order	Higuchi	Peppas	
		r value	r value	r value	n value	r value
1	**F1**	0.854	0.961	0.982	0.990	0.976
2	**F2**	0.869	0.992	0.889	0.960	0.966
3	**F3**	0.852	0.935	0.880	0.944	0.971
4	**F4**	0.885	0.971	0.869	0.988	0.975
5	**F5**	0.884	0.956	0.844	0.994	0.974

Cont…

S. No.	Formulation	Zero order	First order	Higuchi	Peppas	
		r value	r value	r value	n value	r value
6	**F6**	0.792	0.952	0.978	0.875	0.979
7	**F7**	0.886	0.944	0.931	0.835	0.957
8	**F8**	0.874	0.975	0.910	0.989	0.978
9	**F9**	0.906	0.935	0.953	0.899	0.977

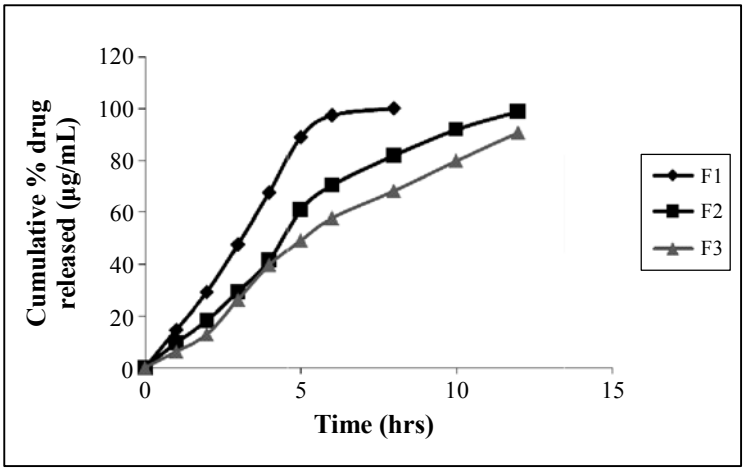

Fig. 1: **Drug release profiles from various matrix formulations F1 to F3**

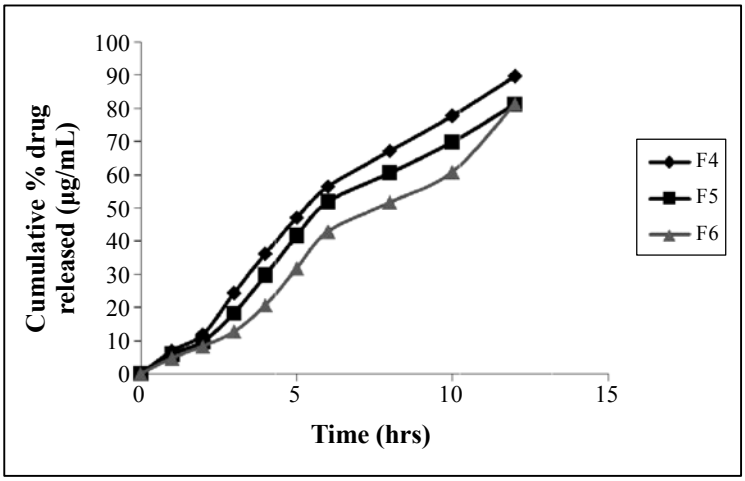

Fig. 2: Drug release profiles from various matrix formulations F4 to F6

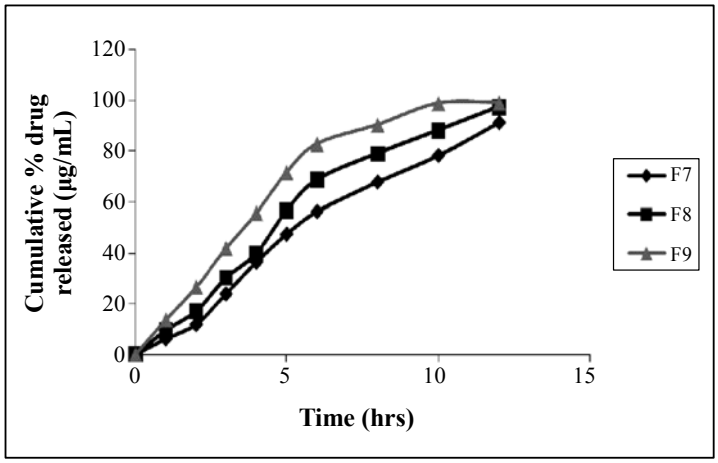

Fig. 3: Drug release profiles from various matrix formulations F7 to F9

RESULTS AND DISCUSSION

Two sets of formulations are initially developed. Set I (F1 to F3) comprises of combination of hydrophobic and hydrophilic polymers and the other Set II (F4 to F6) comprises of hydrophilic polymers only – almond gum and HPMC. The objective of employing such 2 sets is to evaluate any advantage that combined polymers may offer in retarding the release over only the hydrophilic polymers. Contrary to the expectation, it was observed that the matrix tablets containing almond gum (Set II) could retard the drug release (drug release results are discussed in more detail latter) more effectively than the tablets having the combined hydrophobic and hydrophilic polymers.

Precompression characteristics

The Carr Index, Hausner Ratio and the Angle of Repose of the 2 sets of powder blends are determined and the data is shown in Table 2. It was noted that the flow properties of the powder blends of Set II are more favorable than the Set I. The values of Carr Index, Hausner Ratio and the Angle of Repose of set II are found to be lower than the corresponding values of set I. The poor flow of formulations of set I are probably because of the presence of hydrophobic ingredient compritol present in set I. The better flow of the powder blend of set II will probably result in more pharmaceutically acceptable tablets (as is evident in the results shown Table 3) than tablets prepared from set I.

Characterization of matrix tablets

The tablet formulations of all the prepared batches contained levofloxacin within 100 ± 5% of expected content. The hardness of various prepared tablets employing

compritol, i.e. set I is in the range of 4.5-5.0 Kg/cm^2. Whereas the tablets of set II exhibited a higher hardness of 6.0-7.0 Kg/cm^2. Also the friability of the tablets of set II is found to be less than that of set I. These 2 observations could be because of the better flow properties of the formulation set I. The weight variation of the 2 sets of tablets is within pharmacopoeial specifications – and the tablets of set II showed much lesser weight variation. The details of the characteristics of tablet formulations are shown in Table 3.

Drug release

The release of levofloxacin from all the matrix tablets is found to be slow and sustained. In case of set I (F1 to F3), though there is a slow release, the drug was completely released within 6 to 8 hrs itself (F1) as shown in Fig 1. As the proportion of compritol is increased the release also is slowed down and is extended upto 12 hrs (F2 and F3). However the increased compritol is resulting in poor flow of the blend and less than optimum required pharmaceutical characteristics for the matrix tablets that are prepared. Whereas formulations F4 to F6 with no compritol or ethyl cellulose still could prolong the release (Fig. 2) upto 12 hrs. The main difference is the inclusion of the relatively less explored hydrophilic polymer-almond gum. For example formulation F4 showed similar release profile to that of F3. As the proportion of almond gum increased the release is also slowed down (F5 & F6). However even though the release is slow it is also incomplete in the case of formulations F4 to F6.

So to ensure complete release from the matrix tablet-formulation F5 is modified by inclusion of citric acid (SetIII). Levofloxacin is highly soluble in acidic medium and less inalkaline medium. So when the tablet arrives in the intestinal tract there is a possibility of the drug decreasing in its solubility leading to a fall in the diffusion of the drug from the matrix. There are reports that presence of organic acids[9] will modify the drug release from matrix formulations. We designed a matrix formulation by modifying the microenvironment of the swollen matrix by including citric acid the formulation. In the present investigation, it was observed that increasing amounts of citric acid in the matrix formulation resulted in correspondingly higher release (Fig. 3). The presence of citric acid creates a more favorable acidic microenvironment within the swollen gel layer to result in more levofloxacin to dissolve and get released from the matrix ensuring 100% drug release within 12 hrs. Thus from the formulation F8 slow and sustained but complete drug release could be obtained. Whereas in F9 with high citric acid proportion – more than 90% drug release was seen by 8 hours itself. Formulation F2 of set I is found to be comparable to F8 in drug release. But the matrix tablets of set II & III showed more hardness and less friability. (The and hardness and friability details of set III not shown).

Plots of the amount of the drug released vs. square root of time (Fig. 4 to 6) were found to be linear in all the cases indicating the drug release mechanism from the matrix tablets might be of diffusion type as proposed by Higuchi[10]. Accordingly the drug release from these matrix tablets involves penetration of dissolution fluid, dissolution of the drug in dissolution fluid and leaching out of the drug through interstitial channel and pores.

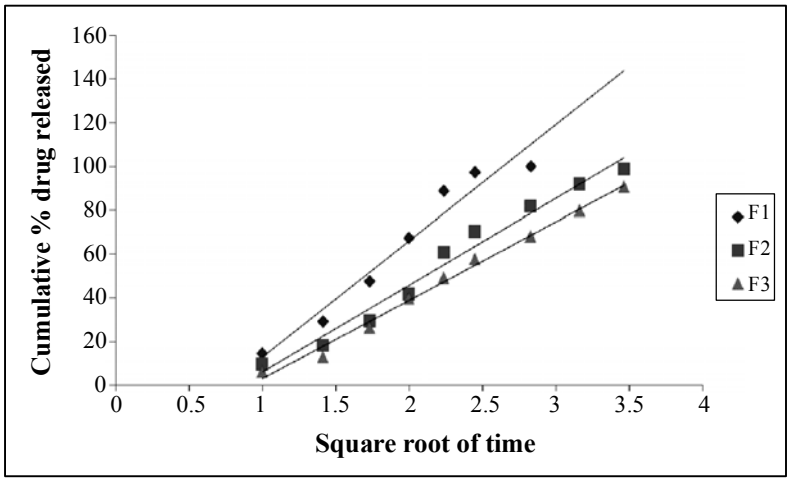

Fig. 4: Higuchi diffusion plot of drug release from matrix formulations, F1 to F3

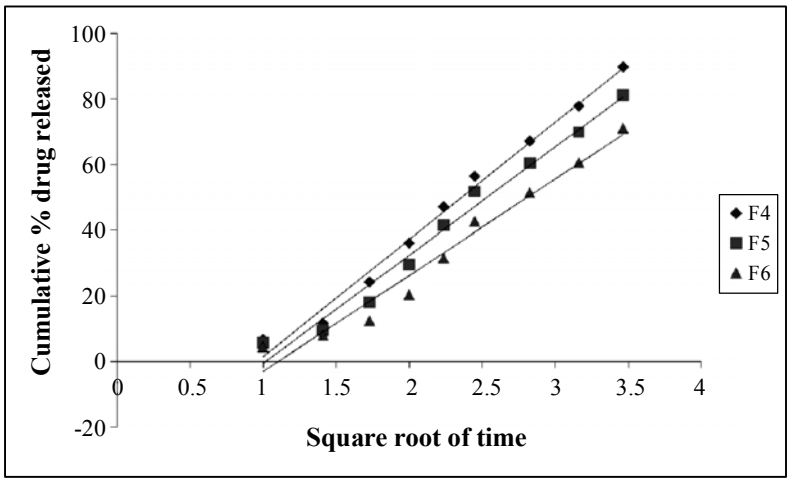

Fig. 5: Higuchi diffusion plot of drug release from matrix formulations, F4 to F6

When the data plotted according to the first-order equation, the formulations showed a good linearity, with significantly higher correlation coefficient values than zero order plots, (0.935 to 0.992). Although, it is desirable for a controlled release device to deliver the drug

in zero-order kinetics, it is extremely difficult to attain such pattern as the kinetics of release is affected by the physicochemical composition of surrounding medium and processing variables. According to the n values (between 0.5 and 1), obtained in the Peppas[11] plot, shown in Table 4, one may conclude that the drug release follows non-Fickiananomalous diffusion.

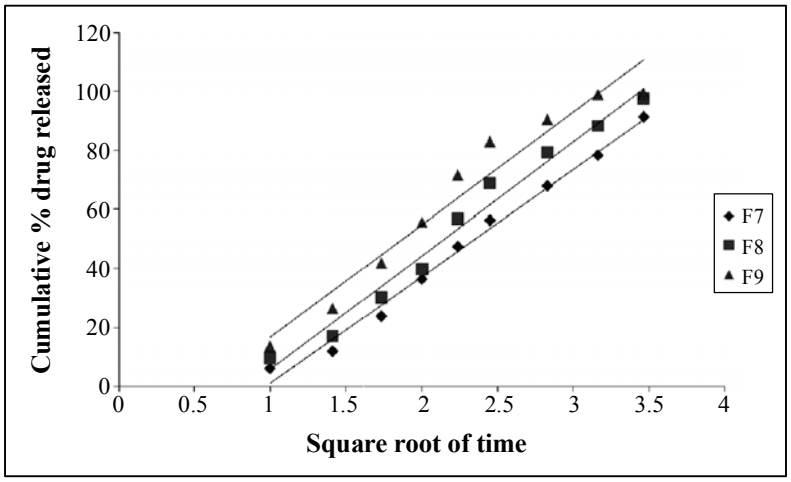

Fig. 6: Higuchi diffusion plot of drug release from matrix formulations, F7 to F9

CONCLUSIONS

(i) Slow and sustained release matrix tablets of levofloxacin could be prepared by employing combined hydrophobic and hydrophilic polymers such as compritol and HPMC.

(ii) The matrix tablets designed by employing only hydrophilic polymers such as almond gum could produce more sustained release than obtained in matrix tablets employing combined polymers.

(iii) The flow properties of the powder blend with almond gum are better than the powder blend obtained with compritol and also the tablets formed from such better flowing powder blends are also found to be pharmaceutically more acceptable.

(iv) The presence of citric acid in the matrix formulations prepared by employing almond gum could enhance the drug release but with changes in the proportion of almond gum and citric acid, matrix tablets could be designed with a slow release spread over 12 hrs.

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