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Comparative evaluation of binders and disintegrants by formulating Lomefloxacin tablets

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Abstract

Lomefloxacin is a broad spectrum anti bacterial agent used in the treatment of respiratory tract and urinary tract infections. Major problem with this drug is its solubility in biological fluids after oral administration. Hence in the present work studies were undertaken on lomefloxacin tablets with an objective of evaluating the effect of formulation variables such as binding agents like gelatin, polyvinyl pyrrolidone, sucrose, starch paste, acacia, methyl cellulose and hydroxy propyl methyl cellulose and disintegrants like dry potato starch, sodium starch glycolate and micro crystalline cellulose on the dissolution rate of lomefloxacin. Among the seven binders added the tablets prepared with hydroxy propyl methyl cellulose, acacia and polyvinyl pyrrolidone were found to be superior with respect to disintegration and dissolution characteristics. Among the three disintegrants added the tablets prepared with dry potato starch are superior with respect to disintegration and dissolution. All formulations were subjected for kinetic analysis, results indicated that all the formulations prepared followed first order release kinetics, formulation containing lomefloxacin with dry potato starch as disintegrant and polyvinyl pyrrolidone as binder (T_2) with a correlation co-efficient of 0.995. The marketed product showed 67.50% of drug release after 45 mins, where as T_2 showed 95.62% of drug release. Formulation T_2 was considered as better when compared to marketed product as far as dissolution efficiency $D.E._{30}$(%) and first order rate constant. Formulation T_2 was also subjected for stability studies as per ICH guidelines and was found to be stable.

Key words: Lomefloxacin, binders, disintegrating agents, tablets.

INTRODUCTION

Lomefloxacin [1] is a relatively new and highly effective broad spectrum anti bacterial agent used in the treatment of respiratory tract and urinary tract infection. Lomefloxacin act by interference with the activity of the bacterial enzyme DNA gyrase which is needed for the transcription and replication of bacterial DNA [2-6]. It is relatively a new drug and slightly

soluble in water. Peak plasma concentration reaches between 2-3 hours. It shows erratic dissolution profile in gastric fluid due to its poor water solubility. Rate of absorption and/or extent of bio-availability for such drug are controlled by rate of dissolution in gastro intestinal fluids. It is reported that the dissolution and bio-availability of a drug from solid dosage form depend much on its formulation additives and method of manufacture or processing variables [7-10]. The peak plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) depend upon extent and rate of dissolution of drug *in vivo* respectively [11]. Hence the present work was aimed at increasing the rate of dissolution of lomefloxacin, by adding appropriate binding agents like gelatin, polyvinyl pyrrolidone, sucrose, starch paste, acacia, methyl cellulose and hydroxy propyl methyl cellulose and disintegrants like dry potato starch, sodium starch glycolate and micro crystalline cellulose. Tablets were prepared by wet granulation technique.

MATERIALS AND METHODS

Materials

Lomefloxacin was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. Gelatin was procured from Rallis, Polyvinyl pyrrolidone from Loba chem.(Mol. Wt. 40,000), Sucrose was sourced from qualigens, Acacia IP, Methyl cellulose(5 cps) and Hydroxy propyl methyl cellulose (5 cps) from Dow chemicals USA, Dry potato starch was procured from Loba chem., Sodium starch glycolate, Micro crystalline cellulose from sigati chloro chemicals, talc and magnesium stearate were of pharmaceutical grade.

Methods: Preparation of lomefloxacin Tablets

Lomefloxacin tablets were prepared by wet granulation method according to the formulae given in Table-1 and 2. A total of nine formulations were prepared. Lomefloxacin and half the amount of the disintegrant were mixed thoroughly in a mortar to obtain a uniform blend. Freshly prepared binding agent solution/ mucilage was then added in small amounts, while mixing the powder blend thoroughly. Sufficient binding agent was added and mixed to obtain a dough mass. The mass was then passed through sieve # 16 to obtain wet granules. The wet granules were dried at 45^0C for about 1 hour. The dried granules were again passed through # 16. Remaining quantity of disintegrant, magnesium stearate and talc were then added to dry granules and blended thoroughly. The granules were then compressed to a hardness of 4-6 kg/sqcm. The prepared tablets were subjected for post compression parameters like uniformity of thickness, hardness, friability, weight variation, drug content uniformity, *in vitro* disintegration and dissolution studies.

Table-1: Formulae of lomefloxacin tablets prepared using different binders

Ingredients per tablet (mg)	Formulations						
	T_1	T_2	T_3	T_4	T_5	T_6	T_7
Lomefloxacin hydrochloride	200	200	200	200	200	200	200
Dry potato starch	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Gelatin	7.5	--	--	--	--	--	--
Poly vinyl pyrrolidone	--	7.5	--	--	--	--	--
Sucrose	--	--	7.5	--	--	--	--
Starch paste	--	--	--	7.5	--	--	--
Acacia	--	--	--	--	7.5	--	--
Methyl cellulose	--	--	--	--	--	7.5	--
Hydroxy propyl methyl cellulose	--	--	--	--	--	--	7.5
Magnesium stearate	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total weight of the tablet (mg)	250	250	250	250	250	250	250

Table-2: Formulae of lomefloxacin tablets prepared using different disintegrating agents

Ingredients per tablet (mg)	Formulations		
	T_2	T_8	T_9
Lomefloxacin hydrochloride	200	200	200
Poly vinyl pyrrolidone	7.5	7.5	7.5
Dry potato starch	37.5	--	--
Sodium starch glycollate	--	12.5	--
Micro crystalline cellulose	--	--	37.5
Magnesium stearate	5.0	5.0	5.0
Total weight of the tablet (mg)	250	225	250

***Invitro* disintegration time**

Disintegration time of tablets were determined in distilled water using Thermonik tablet disintegration test machine of USP standard. The results are given in Table-3.

Table- 3: Hardness, friability and disintegration characteristics of Lomefloxacin tablets prepared using different binders, disintegrating agents and commercial formulation

Sl.No.	Tablet formulation	Hardness (Kg/sq cm)	Friability (% wt. loss)	Disintegration time (mins)
T_1	Lomefloxacin with gelatin	5.3	0.6	11
T_2	Lomefloxacin with PVP	5.5	0.5	12
T_3	Lomefloxacin with sucrose	3.9	0.8	07
T_4	Lomefloxacin with starch paste	4.1	0.7	06
T_5	Lomefloxacin with acacia	4.7	0.7	12
T_6	Lomefloxacin with Methyl cellulose	6.8	0.4	> 30
T_7	Lomefloxacin with HPMC	4.0	0.8	15
T_8	Lomefloxacin with PVP & SSG	4.8	0.7	08
T_9	Lomefloxacin with PVP & MCC	6.1	0.9	05
C_1	Lomefloxacin Tablets	4.8	0.7	06

***Invitro* dissolution studies**

Dissolution of lomefloxacin from the tablet formulations was studied in USP XXIII dissolution rate apparatus (M/s DBK electronics) employing a basket type 900 ml of 0.1N hydrochloric acid was used as the dissolution medium.The basket was adjusted to rotate at 50 rpm. A temperature of 37 ± 1^0C was maintained throughout the experiment. One tablet was used in each test. 5ml aliquots were withdrawn at different time intervals and replaced with fresh quantity of dissolution medium. The samples withdrawn were suitably diluted and assayed for lomefloxacin spectrophotometrically at 286.4nm. Percent of lomefloxacin dissolved at various time intervals was calculated and plotted against time. The results are given in Table-4. For comparison, the dissolution rate of lomefloxacin from commercial tablets was also studied as described above. The results are given in Table-4 and shown in Fig 1 & 2.

Table-4 : Dissolution characteristics of various tablet formulations prepared with different binding, disintegrating agents and commercial formulation

S. No.	T_{50} (min)	Percent dissolved		D.E.$_{30}$ (%)	K_1 (min^{-1})
		30 min	60 min		
T_1	> 2 hrs	15	24	9.06	0.00575
T_2	12	86	101	50.0	0.0575
T_3	14	79	94	47.5	0.09212
T_4	18	79	99	40.31	0.1036
T_5	08	90	101	61.0	0.09212
T_6	> 2 hrs	20	29	12.5	0.00460
T_7	10	90	96	67.5	0.1151
T_8	15	56	72	38.75	0.0287
T_9	18	33	72	23.75	0.02303
C_1	25	59	74.85	30.62	0.02303

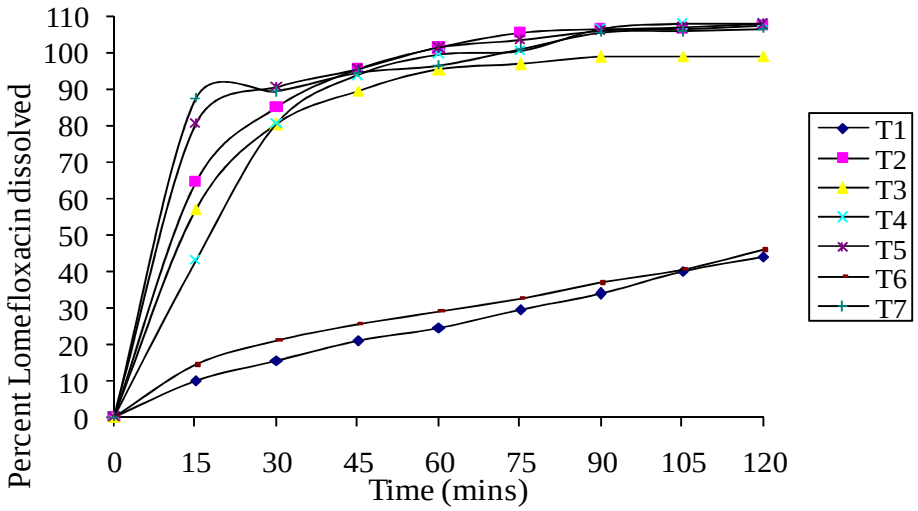

Figure 1: Dissolution profiles of lomefloxacin hydrochloride tablets prepared employing different binders

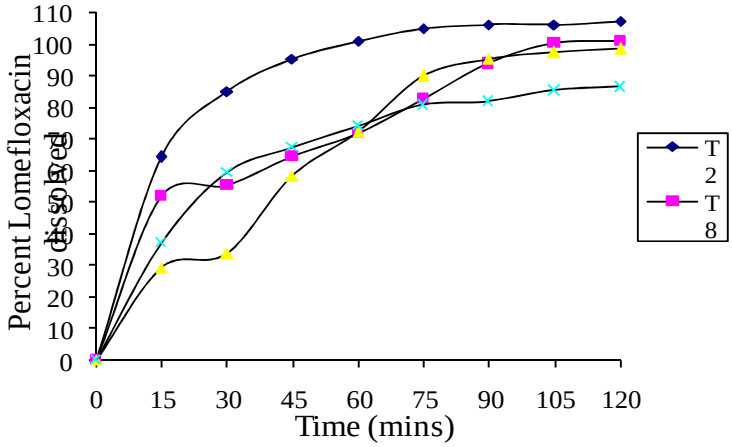

Figure 2: Dissolution profiles of lomefloxacin hydrochloride tablets prepared employing different disintegrants and commercial formulation

RESULTS AND DISCUSSION

In the present study lomefloxacin tablets were prepared by using seven binding agents namely gelatin, polyvinyl pyrrolidone, sucrose, starch paste, acacia, methyl cellulose and hydroxy propyl methyl cellulose. All the binders were used at a concentration of 3% of the formula in the form of either an aqueous solution or mucilage. All the tablets contained 15% of dry potato starch as disintegrant (T_1-T_7), formulation T_8 and T_9 contained sodium starch glycollate (5% w/w) and microcrystalline cellulose (15% w/w) as disintegrant respectively with polyvinyl pyrrolidone as binding agent. IR spectroscopy was used as means of studying drug excipient compatibility and confirmed undisturbed structure of lomefloxacin, which indicated no drug excipient interaction. The data obtained of post compression parameters such as hardness, friability, weight variation, drug content, invitro disintegration are shown in Table-2. The hardness was found to be in the range of 3.9 to 6.8 kg/cm^2. All the formulations indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value was found to be less than 1% limits. All the tablets passed weight variation test as the percent weight variation of all the tablets was found to be uniform with low SD. values indicating efficient mixing of drug, disintegrant and excipients. The percentage drug content of all the tablets was found to be between 96.45±1.23% and 104.28±1.82% of lomefloxacin, which was within the acceptable limits. The results of *in vitro* disintegration of all the tablets were found to be within the range of 05-15 mins except formulation T_6 containing methyl cellulose as binder which failed to fulfill the official disintegration test limit (> 30 mins). Marketed formulation (C_1) showed a disintegration time of 06 mins. It was observed that when microcrystalline cellulose and sodium starch glycollate was used as disintegrant, the tablet disintegrates rapidly may be due to its inherent disintegration capacity when compared to other tablets prepared by using dry potato starch. All the tablets prepared were subjected for *in vitro* dissolution test. Dissolution characteristics of various tablet formulation prepared with different binding and disintegrating agents are given in Table-4. Dissolution profiles of lomefloxacin tablets prepared employing different binding agents, disintegrants and commercial formulation are given in figure 1 and 2 respectively. The tablets prepared using hydroxy propyl methyl cellulose (T_7), acacia (T_5), polyvinyl pyrrolidone (T_2), sucrose (T_3) and starch paste (T_4) exhibited good dissolution characteristics and gave rapid dissolution of lomefloxacin. The T_{50} values were found to be in the range of 8-18 mins and percent dissolved in 30 mins ranged from 79 to 90 % with these tablets. The D.E.$_{30}$ (%) for all the formulations ranged from 40-67.5 %, where as tablets prepared using methyl cellulose (T_6) and gelatin (T_1) as binders gave very poor dissolution of lomefloxacin [12]. The percent dissolved in 60 min was found to be 12.9 and 9.0 respectively for tablets T_6 and T_1. Based on T_{50} and D.E.$_{30}$(%). values the following is the order of increasing dissolution rate character of the tablets prepared with various binding agents.

Hydroxy propyl methyl cellulose (T_7) > acacia (T_5) > polyvinly pyrrolidone (T_2) > sucrose (T_3) > starch paste (T_4) > methyl cellulose (T_6) > gelatin (T_1). It was observed during the dissolution rate test that the tablets prepared using gelatin and methyl cellulose as binders remained intact and did not disintegrate. Hence the binding agent effects seem to be much dependent on disintegration of the tablet and the generation of surface area for dissolution.

Thus hydroxy propyl methyl cellulose, acacia and polyvinyl pyrrolidone were found to be good binding agents for lomefloxacin tablets. The dissolution of lomefloxacin from all the tablets both formulated and commercial followed first order kinetics. The correlation co-efficient values was found to be 0.995 for formulation T_2 with a first order rate constant (K_1) of 0.0575 min^{-1}. To evaluate the influence of disintegrants on the dissolution rate of lomefloxacin from tablets,

tablets were prepared using poly vinyl pyrrolidone (3% w/w) as binding agent with three disintegrants dry potato starch (15% w/w) T_2, sodium starch glycollate (5% w/w) T_8,and micro crystalline cellulose (15% w/w) and T_9 formulation respectively. Tablets prepared with dry potato starch (T_2) gave relatively rapid dissolution of lomefloxacin and tablets prepared with micro crystalline cellulose (T_9) gave slow dissolution. The dissolution of lomefloxacin from these tablets also followed first order kinetics. The following is the order of increasing dissolution rate with various disintegrants.

Dry potato starch > sodium starch glycollate > micro crystalline cellulose.

CONCLUSION

Tablets prepared using hydroxy propyl methyl cellulose, acacia, polyvinyl pyrrolidone, sucrose and starch paste as binders exhibited good dissolution characteristics and gave rapid dissolution of lomefloxacin. Tablets prepared with methyl cellulose and gelatin exhibited poor dissolution of lomefloxacin. Overall hydroxy propyl methyl cellulose, acacia and poly vinyl pyrrolidone were found to be good binding agents for lomefloxacin tablets. Among the three disintegrants studied dry potato starch gave relatively rapid dissolution of lomefloxacin followed by sodium starch glycollate and micro crystalline cellulose. The effect of binders and disintegrants seem to be much dependent on disintegration of the tablets and the generation of surface area for dissolution.

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