

The Effect of Tablet Formulation and Hardness on *in Vitro* Release of Cephalexin from Eudragit L100 Based Extended Release Tablets

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Eighteen batches of cephalexin extended release tablet were prepared by wet granulation method by using Eudragit L100. The effect of the concentration of Eudragit L100, microcrystalline cellulose and tablet hardness on cephalexin release was studied. The formulated tablets were also characterized for physical and chemical parameters. The dissolution results showed that a higher amount of Eudragit in tablet composition and higher tablet hardness resulted in reduced drug release. An increased amount of microcrystalline cellulose in tablet composition resulted in enhanced drug release. Tablet composition of 13.3% w/w Eudragit L100 and 6.6 to 8% w/w microcrystalline cellulose with hardness of 7–11 kg/cm² gave predicted release for 6 h. The *in vitro* release was compared with a marketed tablet. Physical and chemical parameters of all formulated tablets were within acceptable limits. The effect of storage on *in vitro* release and physicochemical parameters of tablets was evaluated and two batches among formulated eighteen batches found to be in acceptable limits.

Key words cephalexin; extended release tablet; Eudragit L100; microcrystalline cellulose; tablet hardness

Cephalexin is a semi synthetic antibiotic derived from cephalosporin 'C'. It is absorbed completely (80–100%) after oral administration¹⁾ and having a biological half-life²⁾ of 1 h. To maintain therapeutic range, the drug should be administered 3–4 times a day, which leads to saw tooth kinetic and resulting in ineffective therapy.^{3–5)} Hence, we attempted to formulate extended release tablet, which can provide constant effective drug level for six hours, based on calculations considering pharmacokinetic parameters.

The main objectives of the present work was to formulate cephalexin extended release tablets by using Eudragit L100 and to study the effect of polymer concentration and hardness on dissolution profile. The tablets were characterized by drug content, weight variation, hardness, thickness, friability, and stability. The *in vitro* release of formulated extended release tablet was compared with a marketed cephalexin extended release tablet.

MATERIALS AND METHODS

Materials Cephalexin IP, Orchid Chemicals and Pharmaceutical Ltd., India. Eudragit L100 NF, Vikram Thermo (India) Ltd. Polyvinylpyrrolidone (PVP), Plaskol, Shanghai Sun Power New Material Company, China. Magnesium stearate IP, Sinai Pharma Pvt Ltd., India. Microcrystalline cellulose powder (MCCP) IP, Sigma Chichlro Chemicals Pvt. Ltd., India. Lactose IP, Lactose India Ltd. All other chemicals used were of analytical grade.

Machineries Tablet compression machine, Cadmach Machinery Co. Pvt. Ltd. UV-visible spectrophotometer, UV-2201 Shimadzu. Programmable Tablet dissolution tester USP XXI and XXII, TDT 067, ELECTROLAB. Sonicator, Branson, SmithKline. Karl-Fischer titrator, Precision V/M MD. Friability test apparatus, Indian Equipment Corporation. Tablet Disintegration test machine IP/BP/USP standard, Campbell Electronics. Tablet hardness tester, DrSchleuniger Pharmatron.

Theory. Determination of Cephalexin Dose for Extended Release⁶⁾ The dose of cephalexin required for initial and sustained delivery is calculated by considering phar-

macokinetic parameters of cephalexin.^{1,2)}

Biological half life ($t_{1/2}$) = 1 h

First order elimination rate constant $K_{el} = 0.693/t_{1/2}$

Time to reach peak plasma concentration $T_p = 1$ h

Volume of distribution $V_d = 15$ l

Desired therapeutic concentration (DTC) for 125 mg dose = 4.5 mg/l

Time for which drug is to be released from extended dose $T = 6$ h

Desired constant release rate K_r^0 (zero order release)

$$K_r^0 = K_{el} \times V_d \times \text{DTC} \quad (1)$$

$$K_r^0 = 0.693/1 \times 15 \times 4.5 = 46.7 \text{ mg/h}$$

$$DT = DI^* + DS \quad (2)$$

Where, DT is total dose, DI* is corrected initial dose, DS is sustained dose

$$\begin{aligned} DS &= K_r^0 \times T \\ &= 46.7 \times 6 = 280.7 \text{ mg} \end{aligned} \quad (3)$$

Amount of drug released from maintenance dose during release of initial dose (Till peak plasma concentration achieved)

$$= K_r^0 \times T_p \quad (4)$$

$$= 46.7 \times 1 = 46.7 \text{ mg/h}$$

$$DI^* = DI - 46.7$$

$$DI^* = 125 - 46.7 = 78.3 \text{ mg}$$

$$DT = DI^* + DS$$

$$DT = 78.3 + 280.7 = 359 \text{ mg}$$

Total dose for extended release formulation = 359 mg

Adjusted to 375 mg.

Formulation of Cephalexin Extended Release Tablets The cephalexin extended release tablets were prepared by wet granulation technique with various ratios of Eudragit

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L100 as per the formula given in Table 1.

The drug cephalexin was passed through sieve #40. The additives Eudragit L100 and microcrystalline cellulose were passed through sieve #60. They were mixed in a double cone blender and granules were prepared by wet granulation⁷⁾ method. Polyvinylpyrrolidone in isopropyl alcohol was used as binding agent. The wet granules were dried at room temperature and the moisture content was determined by Karl Fischer method. The dried granules were passed through sieve #14, lubricated with magnesium stearate and compressed using 15/32 flat punches to get tablets.

Batches 1, 2, 3 and 6 were prepared by using different ratio of Eudragit L100 as per the formula given in Table 1. Batches 4 and 5 were prepared by changing the amount of microcrystalline cellulose powder in order to study its effect on release profile. To study the effect of hardness on release profile, in each batch, three sub-batches A, B, and C were prepared with hardness of 5–7, 7–9 and 9–11 kg/cm² respectively.

Evaluation of Formulated Cephalexin Extended Release Tablets. Physical Parameters The formulated tablets were tested^(8,9) for moisture content, weight variation, thickness, friability, hardness, and disintegration.

Drug Content Twenty tablets were weighed and powdered. The quantity equivalent to 100 mg of cephalexin was weighed accurately and taken in 100 ml volumetric flask. Fifty milliliters of water was added, sonicated for 5 min, made up to 100 ml with water, and filtered. Two ml of above solution was diluted to 100 ml in a volumetric flask and estimated at 261 nm.

In Vitro Release Studies The *in vitro* release of cephalexin from formulated tablets were carried out at 0.1 N HCl for 1 h, and continued in 0.01 N HCl for another 1 h and finally in phosphate buffer pH 7.4 for 4 h. The studies were performed in USP dissolution apparatus 1 at 37±2 °C and 100 rpm. Samples were taken at hourly intervals and analysed for cephalexin content⁵⁾ at 261 nm by using UV-visible spectrophotometer. The same procedure was followed to study the *in vitro* release of cephalexin from a marketed product.

Stability Studies The formulated cephalexin tablets, batch 3 and 4, which gave *in vitro* drug release complying the calculated limits, were kept for a short term accelerated stability study in high density polyethylene sealed cover at 40±2 °C/75±5% RH for three months as per "International Congress on Harmonisation States" (ICH) guidelines. Samples were withdrawn for every month of storage and evaluated for appearance, hardness, drug content, dissolution, and disintegration.

RESULTS AND DISCUSSION

The present study involves formulation and development of cephalexin tablet that releases the drug with predicted rate for 6 h. We formulated 1–6 batches of cephalexin extended release tablets by wet granulation method as per formula given in Table 1, to study the effect of Eudragit L100, MCCP and tablet hardness on drug release profile. The amount of percentage of polymer added in each batch is shown in Table 1.

Batches 1, 2, 3 and 6 were prepared to study the influence

Table 1. Composition of Cephalexin Extended Release Tablets

Ingredients mg/tablet	Batch ^{a)} no.					
	1	2	3	4	5	6
Cephalexin IP equivalent to anhydrous cephalexin	375	375	375	375	375	375
Eudragit L100	40	45	50	50	50	60
MCCP	25	25	25	30	20	25
PVP	8	8	8	8	8	8
Magnesium stearate	5	5	5	5	5	5
% of Eudragit with respect to cephalexin	10.6	12	13.3	13.3	13.3	16
% of MCCP with respect to cephalexin	6.6	6.6	6.6	8	5.3	6.6

a) In each batch three sub batches A, B and C were prepared with hardness of 5–7, 7–9 and 9–11 kg/cm² respectively.

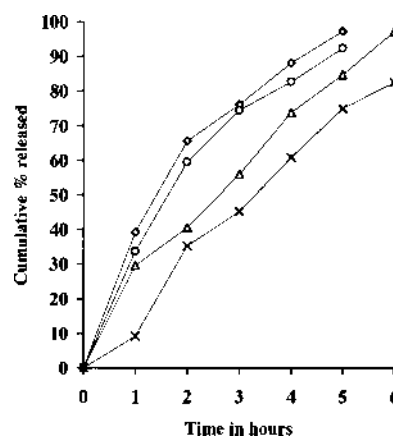


Fig. 1. Influence of Eudragit L100 on *in Vitro* Release of Cephalexin

The figure illustrates the *in vitro* drug release from batch 1B (◇), 2B (○), 3B (△) and 6B (×) tablets formulated with 10.6, 12, 13.3 and 16% of Eudragit L100, with a hardness of 7–9 kg/cm². Each data represents average of six readings.

of quantity of Eudragit L100 in tablets on *in vitro* release. Figure 1 shows the cephalexin cumulative percentage released versus time for tablets formulated with various percentage of Eudragit L100 and having a hardness of 7–9 kg/cm². All formulations tested showed a sustained release over 4–6 h. The release rate of tablets prepared with higher quantity of Eudragit was slower. Faster release rate was obtained by reducing the quantity of Eudragit L100 in the formulation as shown in the Fig. 1. The higher percentage of Eudragit L100 reduces the permeation of water inside the granules and thus produces slower release. The similar effect was observed on batches 1, 2, 3 and 6 prepared with hardness of 5–7 and 9–11 kg/cm².

In batches 3, 4 and 5 the quantity of MCCP incorporated was varied, to find out its effect on the drug dissolution profile. *In vitro* release of cephalexin from tablet formulations, prepared with various percentage of MCCP with a hardness of 7–9 kg/cm² are shown in Fig. 2. The drug release was increased in higher quantity of MCCP, which is acting as pore forming and disintegrating agent, thus produces slower release in lower concentrations. The same effect was observed on batches 3, 4 and 5 prepared with hardness of 5–7 and 9–11 kg/cm². MCCP enhances the permeation of dissolution medium in to polymeric granules and produces rapid release in tablets formulated with higher percentage of MCCP

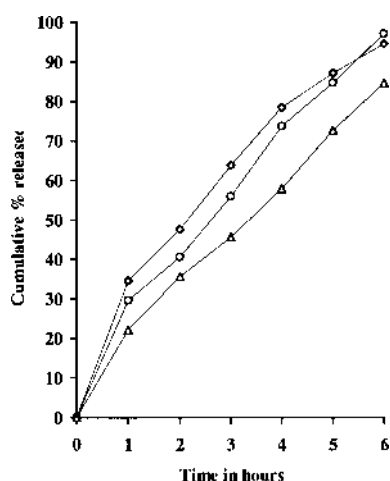


Fig. 2. Influence of Microcrystalline Cellulose on *in Vitro* Release of Cephalexin

The figure illustrate the release of cephalexin from batch 3B ($\diamond$), 4B ($\circ$) and 5B ($\triangle$) tablets having 8, 6.6 and 5.3% of microcrystalline cellulose and a hardness of 7–9 kg/cm². Each data represents average of six readings.

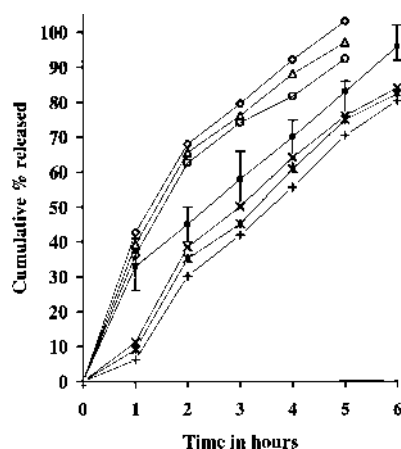


Fig. 3. *In Vitro* Release of Cephalexin from Batch 1A ($\diamond$), 1B ($\triangle$), 1C ($\circ$), 6A ($\times$), 6B ($*$) and 6C ($+$) Tablets

Sub batches A, B and C indicates a hardness of 5–7, 7–9 and 9–11 kg/cm². The release is compared with calculated theoretical release profile ($\blacksquare$). Each data represents average of six readings and the bar represents calculated theoretical release limits.

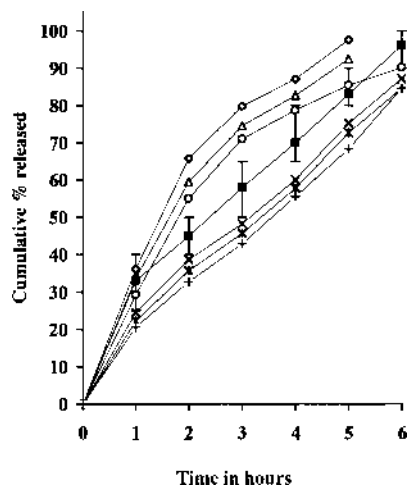


Fig. 4. *In Vitro* Release of Cephalexin from Batch 2A ($\diamond$), 2B ($\triangle$), 2C ($\circ$), 5A ($\times$), 5B ($*$) and 5C ($+$) Tablets

Sub batches A, B and C indicates a hardness of 5–7, 7–9 and 9–11 kg/cm². The release is compared with calculated theoretical release profile ($\blacksquare$). Each data represents average of six readings and bar represents calculated theoretical release limits.

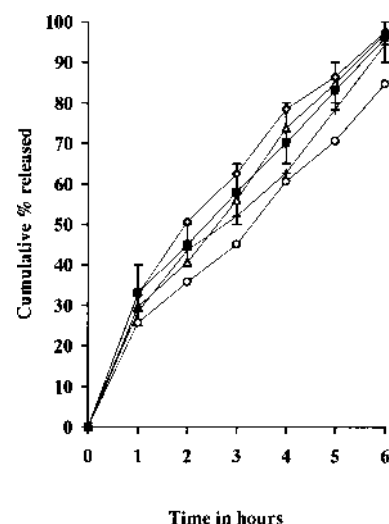


Fig. 5. *In Vitro* Release of Cephalexin from Batch 3A ($\diamond$), 3B ($\triangle$) and 3C ($\circ$) Tablets with Hardness of 5–7, 7–9 and 9–11 kg/cm²

The release is compared with calculated theoretical release profile ($\blacksquare$) and a marketed sample ($+$). Each data represents average of six readings and bar represents calculated theoretical release limits.

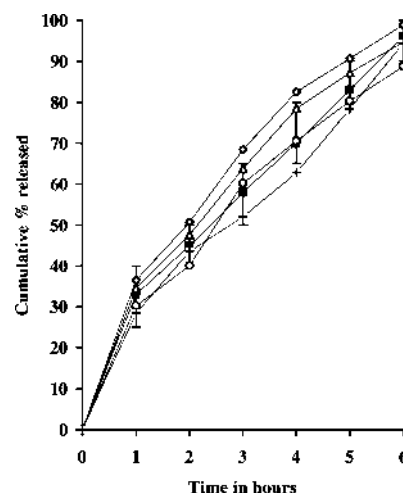


Fig. 6. *In Vitro* Release of Cephalexin from Batch 4A ($\diamond$), 4B ($\triangle$) and 4C ($\circ$) Tablets with Hardness of 5–7, 7–9, 9–11 kg/cm²

The release is compared with calculated theoretical release profile ($\blacksquare$) and a marketed sample ($+$). Each data represents average of six readings and bar represents calculated theoretical release limits.

as shown in Fig. 2.

In each batch, three sub batch tablets A, B and C were prepared with the hardness of 5–7, 7–9 and 9–11 kg/cm², in order to get required release profile and to study the effect of hardness on release profile. The drug dissolution profile of batch 1 to 6 and their sub-batches A, B and C are shown along with theoretical release pattern in Figs. 3 to 6. As expected the increase in hardness resulted in slower release rate. This may be due to slower penetration rate of water into polymer matrix of granules. Higher hardness tablets will contain compact mass of polymer with relatively less pore, resulting in slower release. The elongation of disintegration time at higher hardness further assists slower release. We found that, batch 3A, 3B, 4B and 4C were in accordance with the required theoretical drug release profile and their release was compared with the dissolution profile of a marketed ex-

Table 2. Physical and Chemical Parameters of Formulated Cephalexin Tablets

Evaluated parameters	Batch 1			Batch 2			Batch 3			Batch 4			Batch 5			Batch 6		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Hardness (kg/cm ²)	5—7	7—9	9—11	5—7	7—9	9—11	5—7	7—9	9—11	5—7	7—9	9—11	5—7	7—9	9—11	5—7	7—9	9—11
Average weight (mg)	489	490	492	494	495	495	510	510	503	499	503	500	480	488	486	488	489	493
Thickness (mm)	3.9	3.8	3.7	3.9	3.8	3.7	3.8	3.7	3.5	3.6	3.5	3.4	3.9	3.9	3.6	3.9	3.6	3.5
Friability (%)	0.9	0.8	0.7	0.9	0.8	0.8	0.5	0.4	0.3	0.8	0.7	0.6	0.9	0.9	0.9	0.8	0.9	0.8
Disintegration time (min)	3.5	4	5	5	11	12	8.0	8.2	8	5.5	6	7	7	7	8	8.5	9	9.5
Assay (%)	97.6	98.4	98.6	94.5	95.3	96.5	99.7	99.7	98.5	98.6	99.5	98.6	99.2	99.2	97.6	95.7	96.4	97.6
Moisture content		4.7			4.9			4.5			4.5			4.7			4.8	

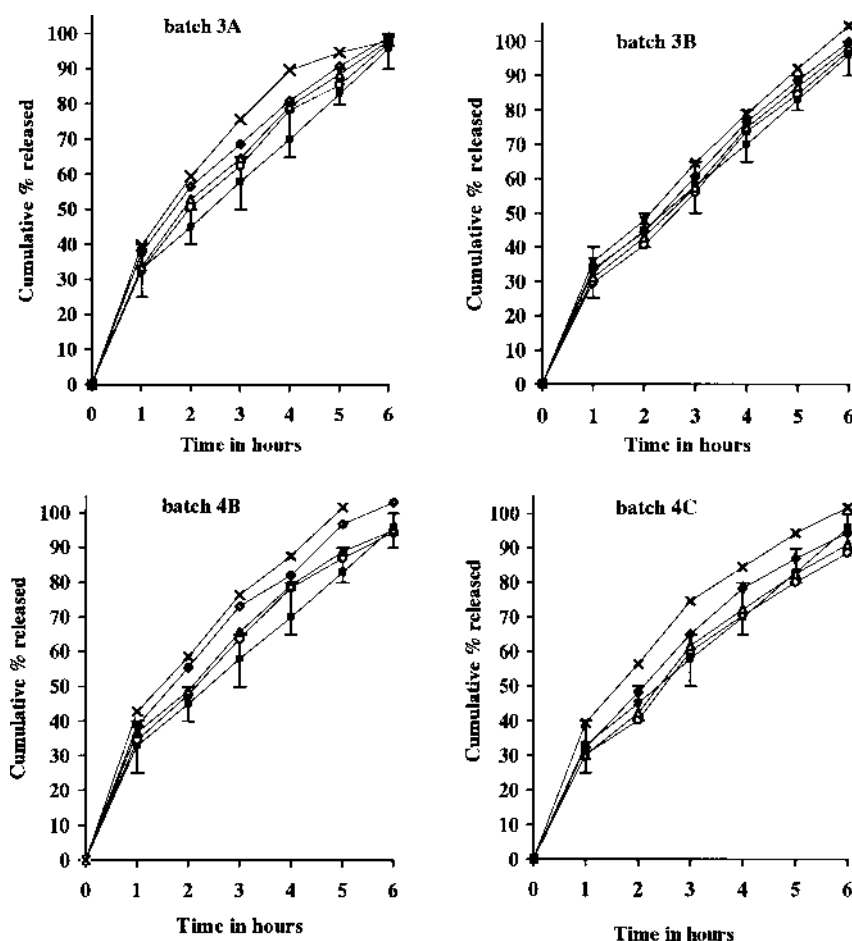


Fig. 7. Initial (○), First Month (△), Second Month (◇) and Third Month (×) *in Vitro* Release Profile of Batches 3A, 3B, 4B and 4C during Stability Studies. The release is compared with calculated theoretical release profile (■). Each data represents average of six readings and bar represents calculated theoretical release limits.

Table 3. Physical and Chemical Parameters of Formulated Cephalexin Tablets during Stability Studies

Batch No.	Time	Appearance	Hardness (kg/cm ²)	% Drug content	Disintegration time (min)
3B	Initial	Pale yellow	7—9	99.7	8.2
4B		Pale yellow	7—9	99.5	6
3B	After 30 d	Pale yellow	6.5—8.5	96.5	8
4B		Pale yellow	6.5—8.5	95.8	5.6
3B	After 60 d	Pale yellow	6—8	90.5	7.5
4B		Pale yellow	6—8	84.5	5.0
3B	After 90 d	Pale yellow	5—7	84.8	5.0
4B		Pale yellow	5—7	79	3.8

tended release tablet (Figs. 5, 6).

All other evaluation parameters like disintegration time, friability, weight variation, thickness and drug content were

studied. All batches passed the acceptable limits of their respective parameters as shown in Table 2. Accelerated stability studies were performed on batch 3A, 3B, 4B and 4C as

per ICH guidelines. The cephalixin content and *in vitro* release was tested at periodic time intervals. The drug release rate becomes fast when stored under accelerated condition as shown in Fig. 7. This may be because of the weakening of polymer matrix present in the granules as evidenced by the decrease in hardness during stability studies as shown in Table 3. *In vitro* release from the batches 3B and 4C were found to be within predicted release profile, and only these two batches (among formulated eighteen batches) were found to be stable for the tested period under accelerated storage conditions. All the other tested parameters of these two batches, is in acceptable limits, and found to be suitable formulation for cephalixin extended release.

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