

Formulation and evaluation of controlled release antibiotic biodegradable implants for post operative site delivery

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Biodegradable implants of ciprofloxacin hydrochloride for post operative site delivery were prepared using glyceryl monostearate and different concentrations of polyethylene glycol (PEG 6000), glycerol and Tween 80 as erosion enhancers by compression and molding technique. Formulations were subjected to *in vitro* drug release by the USP dissolution method, while promising formulations were subjected to *in vitro* drug release by the agar gel method and also to stability studies. It was observed that glyceryl monostearate formed hydrophobic matrix and delayed the drug delivery. Antibiotic release profile was controlled by using different combinations of erosion enhancers. The formulation prepared by the compression method showed more delayed release compared to formulations prepared by the molding method.

Keywords: biodegradable antibiotic implants, glyceryl monostearate, controlled drug release, site delivery, erosion enhancers

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Systemic administration of antibiotics is an inherently inefficient method for achieving high local tissue concentration, because the vascular system distributes antibiotics uniformly throughout the entire body, only a fraction of the given dose reaches the site of infection (1). Direct application and local infusion of antibiotics into the surgical wound has been found to be more effective. However, the rapid absorption of antibiotics from the wound site reduces the duration of protection against infection, and local infusion is cumbersome and requires continuous medical attention. A biodegradable dosage form, which could be implanted at the site of surgical incision to release the drug over an extended period of time could be such a method. Extensive work has been done using poly D,L-(lactide-co-glycolide) and its derivatives as biodegradable polymer matrices; however, very little work was conducted using non-polymeric materials as biodegradable matrices. The implants containing poly D,L-(lactide-co-glycolide), Tween or Span and tomsulosin hydrochloride were prepared and their release was observed for up to 10 days by Mamun *et al.* (2). Localized treatment of osteomyelitis by 6-week release of

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ciprofloxacin from implants using poly (D,L-lactide-co-glycolide) (50:50) was reported by Ramchandani *et al.* (3). A biodegradable long-acting contraceptive capsule-type implant was developed using biodegradable polyester, polycaprolactone as the principle matrix and a water-leachable polyether, Pluronic F68, as drug releasing enhancer (4). Levonorgestrel containing capsules showed an average levonorgestrel release rate of 7.0 μg per day per cm length for a period of 2 years in rats. Baxter Healthcare Corp. (USA) has recently introduced a gentamicin implant using biodegradable polymers which may reduce incidences of surgical site infections and postoperative cast and complications (5).

Guse *et al.* (6) studied mass transport mechanism involved in the control of drug release from a lipid-based implant using different types of triglyceride (glyceryl trilaurate, glyceryl trimyristate, glyceryl tripalmitate and glyceryl tristearate) based cylinders which were prepared by the compression technique. Granules of glyceryl monostearate, polyethylene glycol (PEG 6000) and Tween 80 were mixed with the drug and compressed to form pellets, and then dry coated or compressed with glyceryl monostearate to form implant (7). After initial delay these multilayered implants disintegrate and the compressed mixture of granules containing glyceryl monostearate, polyethylene glycol, Tween 80 and powdered drug are exposed to the dissolution media. This may lead to a pulsatile drug delivery system. To provide a sustained-release drug delivery system the drug might be dispersed in the molten mass of glyceryl monostearate containing a release rate modifier.

In the present study biodegradable sustained-release implants for post operative drug delivery were prepared by dispersing ciprofloxacin hydrochloride in a molten mass of glyceryl monostearate as the biodegradable hydrophobic matrix having different concentrations of erosion enhancers such as PEG 6000, glycerol and Tween 80. To observe the variation in the drug release pattern, the release profile of the compressed formulation was compared with the molded formulation having the same composition and size.

EXPERIMENTAL

Materials

Ciprofloxacin hydrochloride was a gift sample from Adroit Pharmaceuticals Pvt. Ltd. (India), polyethylene glycol, Tween 80, glycerol, agar and potassium dihydrogen phosphate were purchased from Adroit Pharmaceuticals Pvt. Ltd. Glyceryl monostearate was supplied by Suyog Chemicals Pvt. Ltd. (India) and all other chemicals used were of laboratory reagents/analytical reagents grade.

Preparation of antibiotic loaded implants

Compression technique. – Glyceryl monostearate, PEG 6000 and glycerol or Tween 80 in specified quantities (Table I) were heated to 70 °C on a water bath under stirring with a glass rod. The weighed quantity of the drug was dispersed uniformly just before the mass solidified. The solidified blend was stored in freezer for 1 h, the hard mass was ground to fine powder and passed through a sieve (aperture 0.42 mm). The granules were compressed on a rotary compression machine, punch size 8 mm (flat), to form tablet shaped pellets. Different formulations were prepared using various glycerol or Tween 80 concentrations.

Molding technique. – The molten mass and the various formulations were prepared (Table 1) as above, except that the molten mass was drawn up into a 10 mL-syringe and injected into a cylindrical stainless steel mould of 8 mm diameter. The mould was allowed to cool and each cylindrical pellet was cut into 3-mm long pieces equivalent to the thickness of pellets prepared by the compression technique, to make the same size pellets by both techniques.

In vitro evaluation

The release of ciprofloxacin was studied by USP (8) (Disso 2000, paddle method at 50 rpm) at 37 °C in 900 mL of pH 7.4 (0.1 mol L⁻¹) phosphate buffer. Samples were filtered and analyzed spectrophotometrically at 276 nm (Shimadzu 1601, Japan).

Gel simulating in vitro implantation (gel method)

In vitro release was followed by placing the pellet implant in agar gel simulating subcutaneous tissue conditions with respect to viscosity and water content (9). Agar crystals were dissolved in boiling 0.1 mol L⁻¹ phosphate buffer pH 7.4, to prepare 1.5 % an agar solution, which was poured into a Petri dish and left to congeal. A hole (8 mm) was drilled in the center of the agar plate with a cork borer and the pellet/implant was placed in the hole. Sufficient quantity of hot (50-60 °C) agar solution was poured on the top to

Table I. Formulations of compressed and molded implants using erosion enhancers

Sample	Formulation	Ingredient (%)				
		Drug	GMS	PEG 6000	Tween 80	Glycerol
Compressed						
1	C1	20.0	40.0	40.0	0.0	0.0
2	C2	20.0	40.0	37.5	2.5	0.0
3	C3	20.0	40.0	35.0	5.0	0.0
4	C4	20.0	40.0	32.5	7.5	0.0
5	C5	20.0	40.0	37.5	0.0	2.5
6	C6	20.0	40.0	35.0	0.0	5.0
7	C7	20.0	40.0	32.5	0.0	7.5
Molded						
8	M1	20.0	40.0	40.0	0.0	0.0
9	M2	20.0	40.0	35.0	5.0	0.0
10	M3	20.0	40.0	25.0	15.0	0.0
11	M4	20.0	40.0	10.0	30.0	0.0
12	M5	20.0	40.0	10.0	0.0	30.0
13	M6	20.0	40.0	10.0	15.0	15.0

GMS – glyceryl monostearate
PEG 6000 – polyethylene glycol 6000

cover the implants and left to congeal. The plate was covered and placed in the oven (37 °C). Several agar plates implanted with ciprofloxacin devices were prepared at the same time and the samples were collected at 6, 24, 48, 72, 96 h. At each sampling time, one plate was removed from the oven. The plate was divided into four sampling zones and three samples were removed from each zone using a size 4 cork borer (8 mm in diameter). The samples were accurately weighed and dissolved in boiling buffer containing 25 % NaCl. The solution was cooled in an ice bath to precipitate the agar.

Stability studies

Formulations C3 and M2 (both containing 5.0 % of Tween 80, six of each), were wrapped in aluminum foil, sealed and kept for stability studies as per ICH guidelines (10), under conditions 40 ± 2 °C / 75 ± 5 % RH. Every month, one sample from each formulation was withdrawn and estimated for drug concentration. Weighted formulation was crushed and dissolved in 0.1 mol L^{-1} HCl under stirring for 2 h and the drug concentration was calculated.

RESULTS AND DISCUSSION

Formulation prepared by the compression technique C1 (containing 40.0 % PEG 6000) showed up to 59.0 % of drug release in 36 h. Formulation C6 containing 5.0 % glycerol showed 93.8 % of drug release in 36 h compared to 75.2 % from C3 containing the same concentration of Tween 80. Higher drug release from implants containing erosion enhancers may be due to the solubility of erosion enhancers leading to higher porosity of the formulation. Agitation also helps the formulation to disintegrate and provide a larger surface area to enhance drug release. In the case of formulations containing glycerol, higher percentage of drug release was observed because of the higher hydrophilicity of glycerol compared to the formulations containing Tween 80 (Fig. 1a). Increasing the concentration of Tween 80 (C4) or glycerol (C7) from 5.0 to 7.5 % led to soft and sticky formulations causing difficulty in compression; hence these were not used in further studies.

Uncompressed formulations prepared by the molding technique showed faster dissolution due to higher erosion during dissolution. Formulation M1 (containing 40.0 % PEG 6000) showed 73.5 % drug release, while the formulation containing 5.0 % of Tween 80 (M2) showed higher drug release of 81.0 % in 36 h. Formulation M6 containing equal proportions of glycerol and Tween 80 (15.0 % each) showed intermediate release compared to formulations M4 and M5 containing 30.0 % of either Tween 80 or glycerol (Fig. 1b). Delayed drug release from compressed formulations was observed compared to molded formulations, which could be due to the compactness in the dosage form leading to a reduction in porosity, lower erosion and penetration of dissolution fluid into the dosage form.

In vitro drug release kinetics of the formulations prepared by the compression technique (C3) and molding technique (M2) were analyzed by PCP Disso V-3 software (Poona College of Pharmacy, Pune, India).

Considering the release pattern from the formulations C3 (containing 5.0 % of Tween 80) prepared by the compression technique and similar formulation M2 (containing identical percentage of Tween 80) prepared by the molding technique were selected for evaluation by the gel simulation method.

Release of ciprofloxacin hydrochloride from glyceryl monostearate matrixes in the gel method was conducted in order to stimulate the *in vivo* implantation conditions, un-

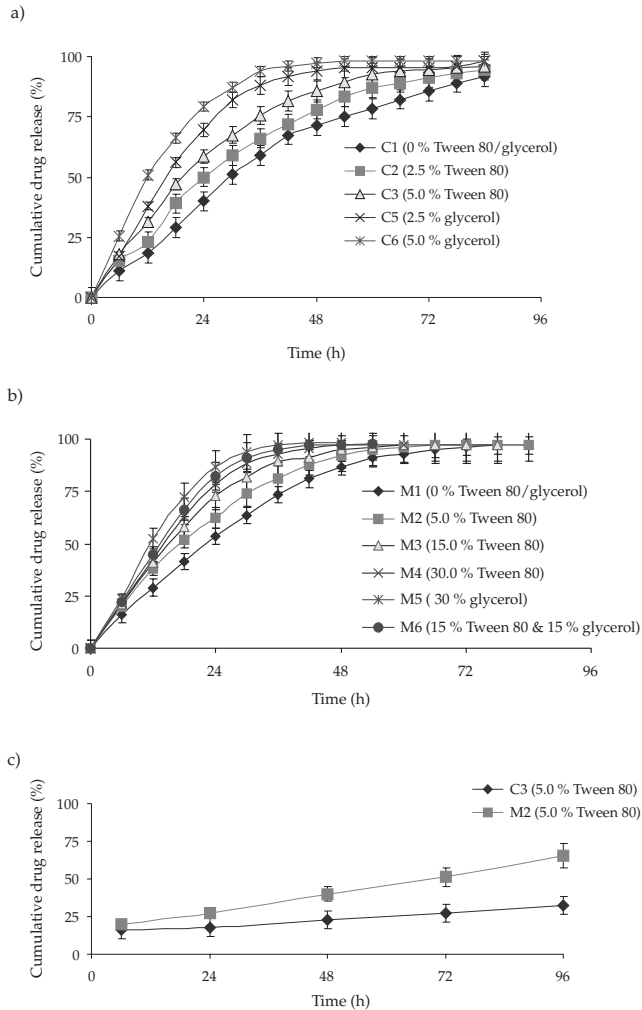


Fig. 1. Comparative *in vitro* ciprofloxacin hydrochloride release profiles from formulations prepared by: a) compression method, b) molding method, c) C3 and M2 (both containing 5.0 % Tween 80) from agar gel. For composition see Table I. Each point denotes mean \pm SD, $n = 3$.

der which the implanted matrixes are surrounded by tissues rather than by aqueous solution. Drug release from the insoluble matrix is generally achieved by penetration of the release medium into the matrix and dissolution of the drug, followed by diffusion of the drug solution through the channels and pores of the matrix.

The drug release from formulations C3 and M2 (both containing 5.0 % Tween 80) in agar gel simulating subcutaneous tissue resulted in significant difference in the drug release pattern compared to the release pattern in dissolution studies. Pellets prepared by the molding technique using 5.0 % Tween 80 (M2) showed 65.5 % higher drug release as compared to the pellets prepared by the compression technique, 32.5 % in 96 h (Fig. 1c). In the agar gel method, drug release taken place by diffusion; a layer close to the implant has higher drug concentration and is inversely proportional to the distance. Percentage diffusion of the drug in the absence of any agitation is also dependent on the solubility of the drug in the aqueous phase.

The commonly adopted model for understanding the release behaviour of the drug from an implant is the Korsmeyer-Peppas equation. The release exponent n is related to the drug release mechanism; the values of 0.6491 and 0.6022 for C3 and M2 (11) resp. indicate anomalous transport (diffusion coupled with the erosion mechanism). R^2 values of linear regression for the Higuchi plot were 0.9852 and 0.9786 for C3 and M2, resp., indicating that the data fit best the Higuchi model.

The values of n in the agar gel method were 0.2441 and 0.4188 for C3 and M2, resp., indicating Fickian transport (diffusion mechanism). The R^2 values for the Higuchi plot were 0.9649 and 0.9885 for C3 and M2, resp. This system was also best presented by the Higuchi model.

In accelerated stability studies, both formulations C3 and M2, having the same composition but differing in the preparation technique, remained stable enough over the designated period under accelerated conditions (40 ± 2 °C/ 75 ± 5 % RH). The initial drug concentration remained constant for a month and dropped by 0.6 and 0.4 %, resp. after 3 months and by 1.5 and 1.3 %, resp. after 6 months.

CONCLUSIONS

On the basis of the results obtained, it can be concluded that glyceryl monostearate forms the hydrophobic matrix for a controlled drug delivery system. Formulations prepared by the compression or molding technique can be implanted subcutaneously at the site of surgery to prevent postoperative infection. The dissolution profile of formulations can be controlled by the use of an erosion enhancer and by the preparation technique. In subcutaneous implantation, the release pattern is dependent on the preparation technique as well as on the solubility of the drug in the aqueous phase.

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S A Ž E T A K

Priprava i vrednovanje biorazgradljivih implantata s kontroliranim oslobađanjem za postoperativnu primjenu

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Biorazgradljivi implantati ciprofloksacin hidroklorida za postoperativnu primjenu pripremljeni su pomoću gliceril monostearata (GMS) i različitih koncentracija polietilen glikola (PEG 6000), glicerola i Tween 80 kao promotora erozije metodom kompresije i lijevanja. Oslobađanje ljekovite tvari iz pripravaka praćeno je *in vitro* prema USP metodi. Pripravci koji su dali dobre rezultate ispitani su i *in vitro* metodom s agarom te su podvrgnuti testovima stabilnosti. Primijećeno je da gliceril monostearat tvori hidrofobni matriks i usporava oslobađanje lijeka. Koristeći različite kombinacije promotora erozije postignuto je kontrolirano oslobađanje antibiotika. Oslobađanje iz implantata dobivenih metodom kompresije sporije je od implantata dobivenih metodom lijevanja.

Ključne riječi: biorazgradljivi implantati antibiotika, gliceril monostearat, kontrolirano oslobađanje, mjesto isporuke, promotor erozije

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