AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

ANTIHYPERTENSIVE BIOADHESIVE DRUG DELIVERY SYSTEM USING COMBINATION OF STARCH WITH POLYMERS

Jain Ankur[1*], Gaud RS[1], Thaker Anil[1], Shende Pravin[1]

1. Dept. of Pharmaceutics, SPTM, SVKM's NMIMS University, Vile Parle (West), Mumbai

ABSTRACT

Mucoadhesive delivery systems were proven to be suitable for the purpose of reduction of transit time of the dosage form through the gastro-intestinal tract, and increasing bioavailability of drug. Buccal tablets of Carvedilol were prepared by direct compression method for using various compositions of combination of Starch: C934 and Starch: HPMCK15M in various ratios. The tablets were evaluated for their characteristics properties, mucoadhesion and in vitro-in-vivo study. All the physicochemical properties were acceptable within the limit. Formulation containing starch and Carbopol 934(E4) showed better bioavailability as compared to tablet containing Starch and HPMCK15 (F5) and The bioadhesive strength of the formulations containing polymers were in the order of E4> F5. Stability studies were carried out as per ICH guidelines and formulations were found to be Stable.

Keywords: Bioadhesive, Buccal tablets, Bioavailability, Bioadhesion, Polymers

*Corresponding Author Email: jain_ankur5@rediffmail.com

Received 20 October 2011, Accepted 21 November 2011

Please cite this article in press as: Jain A *et al.*, Antihypertensive Bioadhesive Drug Delivery System Using Combination Of Starch With Polymers. American Journal of PharmTech Research 2011.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route[1]. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally. Therefore, adhesive mucosal dosage forms were suggested for oral delivery that included adhesive tablets adhesive gels and adhesive patches[2].

Carvedilol was selected as a model drug for the investigation because its oral dose is low (6.25-25mg). The Tmax of Carvedilol is 1.2 hr by oral route, which is long and variable. The dose of Carvedilol is 25mg twice a day, however, a lower effective dose is reported to be approximately 3.125 mg. A suitable buccal drug delivery system should be flexible and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In the present study, the objective was to prepare Mucoadhesive buccal tablets of Carvedilol to prolong the residence time of the buccal tablets, which ensure satisfactory drug release to a mucosa and to avoid loss of drug resulting from wash out with saliva. The buccal tablets were evaluated by weight uniformity, thickness, hardness, surface pH, ex *vivo* mucoadhesive strength, in-vitro drug release studies[1].

MATERIALS AND METHODS

Carvedilol was kindly supplied by Microlab Ltd, Houser, India. Hydroxypropylmethylcellulose K15M, (Signet, Mumbai, India) and Carbopol 934 (Signet, Mumbai, India) were obtained from McW Pharmaceuticals, Indore as gift samples. Pregelatinized starch was supplied by National starch, Mumbai.

Formulation of buccal tablets

Carvedilol was mixed manually in a glass mortar with different compositions (**Table 1(a) and (b)** of Starch: HPMC K15M and Starch: Carbopol 934. The blend was lubricated with magnesium stearate for 3-5 min and then compressed into tablets by direct compression method using 8-mm flat-faced punches. The tablets were compressed using a rotary tablet machine (Karnavati, India).

Table 1(a). Composition of formula Starch: HPMCK15M

Formulations	F1	F2	F3	F4	F5	F6
Ratio	85:15	75:25	60:40	50:50	40:60	25:75
Starch: HPMCK15M	112.55mg	112.55mg	112.55mg	112.55mg	112.55mg	112.55mg
Drug:	6.25 mg	6.25 mg	6.25 mg	6.25 mg	6.25 mg	6.25 mg
Magnesium stearate:	1.2 mg	1.2 mg.	1.2 mg.	1.2 mg.	1.2 mg.	1.2 mg.
Total weight of tablet contain:	120mg	120mg	120mg	120mg	120mg	120mg

Table 1(b). Composition of formula Starch: Carbopol 934

Formulations	F1	F2	F3	F4	F5	F6
Ratio	85:15	75:25	60:40	50:50	40:60	25:75
Starch:Carbopol 934	112.55mg	112.55mg	112.55mg	112.55mg	112.55mg	112.55mg
Drug:	6.25 mg	6.25 mg	6.25 mg	6.25 mg	6.25 mg	6.25 mg
Magnesium stearate:	1.2 mg	1.2 mg.	1.2 mg.	1.2 mg.	1.2 mg.	1.2 mg.
Total weight of tablet contain:	120mg	120mg	120mg	120mg	120mg	120mg

Evaluation of tablets

Thickness

The diameter and thickness of the formulated tablets were measured using Vernier Caliper (lab India, Mumbai).

Assay

The formulated single layered tablet was dissolved in 100ml isotonic phosphate buffer (pH 6.8± 0.2): methanol (9:1). The solution was filtered through 0.45µ filter to remove any undissolved components. The resulted solution was analyzed spectrophometrically at 242 nm by UV spectrophotometer (Perkin Elmer, Germany) [6].

Bioadhesion Study

Fresh sheep buccal mucosa was obtained from a local slaughterhouse (Andheri west, Mumbai) and used within 2 h of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer pH 6.8 at 37^{o}C. Bioadhesive strength of the tablet was measured (n = 3) on a modified physical balance. A piece of buccal mucosa was tied on the upper side of the Teflon block in the glass container, filled completely with isotonic phosphate buffer (pH 6.8, 37±1^{o}C). The tablet was stuck on the bottom side of Teflon which is hanging by ring. The mass, in grams, required to detach the tablet from the mucosal surface gave the measure of mucoadhesive strength[5].

In-vitro dissolution study

The USP XXIV rotating paddle dissolution apparatus (Electrolab, India) was used to study the drug release from buccal patches. The dissolution medium consisted of 200 ml of isotonic phosphate buffer pH 6.8 containing 2% sodium lauryl sulphate. The release was performed at 37 ± 0.5^{o}C, at a rotation speed of 50 rpm. One side of the buccal tablet was attached to a cover slip with instant adhesive (cyanoacrylate). The cover slip was put in the bottom of the dissolution vessel so that the tablet remained on the upper side of the slip. Two ml of samples were withdrawn at pre-determined time intervals (0.5, 1, 2, 3 upto 24h) and replaced with fresh medium to maintain the sink condition. The samples were filtered through 0.45mm membrane filter paper with appropriate dilutions with phosphate buffer pH 6.8 and were assayed spectrophotometrically at 242 nm[7].

In vivo study

In this study a group of 6 healthy rabbits weighing 1.0-1.5kg were used for the study for selected ratio of formulations. Protocol was approved by animal ethical committee (Protocol number: CPCSEA/SPTM/P-49/2008). Rabbits were anaesthetized by diazepam (5mg/kg; i.m). The single layered tablet was applied directly to the buccal pouch of the rabbits after 10min post anesthesia. Conventional marketed tablets (6.25mg) were administered orally to one group to compare the pharmacokinetic parameter after oral and buccal administration. A group of 6 rabbits were used as a control for the experiment. At an interval of 0, 4, 8, 12, 16, and 24h, 0.5-1.0ml of blood was withdrawn via marginal ear vein using 26 gauge needles. The blood was centrifuged at 8000 rpm, 10 min and plasma was collected. Protein separation from the plasma was done by adding equivalent amount of methanol and centrifuged at 10,000 rpm then protein free plasma was collected and analyzed by High Performance Liquid Chromatography (HPLC) using C18 column (Shimadzu, Japan) [9].

Analysis of blood sample

The above protein-free plasma was mixed with 50µl Carvedilol acting as internal standard and 20µl was injected through syringe filter into an isocratic HPLC with UV detector. The column employed was C18 (4.6 x 100mm, 3.5 µm). The mobile phase consisted of methanol: KH_2PO_4, (50:50, v/v) pH 2.5 and flow rate was adjusted to 1.0 ml/min. Area under curve (AUC) of the plasma drug concentration vs. time was determined with trapezoidal rule method, C_{max} and t_{max} were calculated by using software (PK Solution 2.0). The pharmacokinetic data was compared with that obtained from conventional oral tablets[10].

RESULTS AND DISCUSSION:

Physicochemical parameters

The mucoadhesive tablets were loosely compressed on the 12 station mixed tooling machine. The obtained physicochemical parameters of the tablets were recorded in **Table 2**. Diameter of formulated tablets of Starch: HPMC were in the range of 7.4 ±0.057 mm (F1) to 8.0 ±0.1 mm (F6). Thickness was found in the range of 1.5 ±0.05mm to 1.8 ±0.1mm. Hardness was found in the range of 1.5 ±0.05 kg/cm^2 to 1.8 ±0.1 kg/cm^2. The assay values were found to be ranging from 90 ± 0.16% (F1) to 93 ± 0.16% (F6). Diameter of formulated tablets of Starch: Carbopol 934 were in the range of 7.7±0.1mm (E1) to 8.0 ±0.1 mm (E6). Thickness was found in the range of 1.7 ±0.01mm to 2.0±0.05 mm. Hardness were found in the range of 3.3±0.15 kg/cm^2 to 4.8±0.1 kg/cm^2. The Assay value was found to be ranging from 89±0.18 % (E1) to 93 ± 0.16% (E6)[11].

Table 2. Characterization of tablets

Formulation	Ratio	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Assay
F1	85:15	2.0±0.05	1.7 ±0.057	8.0 ±0.1	91 ± 0.24
F2	75:25	2.6 ±0.1	1.6 ±0.057	7.9 ±0.057	93 ± 0.16
F3	60:40	3.2 ±0.05	1.8 ±0.1	7.4 ±0.06	90 ± 0.16
F4	50:50	3.4 ±0.05	1.7 ±0.1	7.4 ±0.057	90 ± 0.19
F5	40:60	4.3 ±0.15	1.6 ±0.05	7.4 ±0.057	92 ± 0.13
F6	25:75	4.4 ±0.15	1.5 ±0.05	7.4 ±0.057	91± 0.14
E1	85:15	3.3±0.15	1.8±0.05	7.9±0.15	96±0.03
E2	75:25	3.6±0.05	1.7±0.05	8±0.1	89±0.18
E3	60:40	3.7±0.1	1.7±0.1	7.9±0.057	92±0.19
E4	50:50	4.5±0.25	1.7±0.05	7.7±0.1	91±0.29
E5	40:60	4.7±0.20	1.8±0.05	7.8±0.1	92±0.30
E6	25:75	4.8±0.1	2.0±0.05	7.9±0.15	91±0.04

Bioadhesive strength

Bioadhesive strength of the formulated tablets of Starch: HPMCK15M (F1 to F6) was determined using a modified physical balance. The mucoadhesive strength of all formulation was shown in **Table 3** which was in the range of 3.2±0.26 g/cm^2 to 18.5±0.44 g/cm^2 and the highest mucoadhesion was found in F5 (40:60). As the concentration of HPMC increases mucoadhesive stress. The test was performed for the formulated tablets of Starch: Carbopol 934 (E1 to E6) by using same procedure for determining the bioadhesive strength on the above mentioned ratios. Bioadhesive profile is shown in the **Table 3**. The mucoadhesive strength of all the formulation was found to be in the range of 10.3±0.29 g/cm^2 to 32.5±0.83 g/cm^2.

The maximum mucoadhesive strength was observed in the formulation E6. It was concluded that as the concentration of Carbopol 934 increases bioadhesive strength also increases strength also increases. This may be attributed to the polymer and mucus interaction with hydrogen bonds. Work of adhesion is suggested to be dependent on the interpenetration of the Carbopol chains into the mucus, while the adhesion force is considered to be dependent on the formation of hydrogen bonds between the functional groups of

Table 3.Bioadhesive strength

Code	Bioadhesive strength (g) n=3 (±SD)	Code	Bioadhesive strength (g) n=3 (±SD)
F1	3.2±0.26	E1	10.3±0.29
F2	4.1±0.28	E2	12.3±0.23
F3	8.3±0.08	E3	14.3±0.28
F4	12.3±0.22	E4	20.5±0.50
F	18.5±0.44	E5	28.4±0.51
F6	16.3±0.80	E6	32.5±0.83

the bioadhesive agents and the mucus. Comparatively HPMCK15M show weaker bioadhesion strength, which may be attributed due to the absence of proton donating carboxyl group which reduces its ability for the formation of hydrogen bond. Starch as having adhesive property showed more adhesion when it is mixed with 50% Carbopol 934.[11]

In vitro dissolution study

Formulations of Starch: HPMC tablets (F1 to F6)

Controlled release profile of developed single layered tablets of Starch: HPMC (F1 to F6) were studied in pH 6.8 buffer. In vitro data and graph of formulated tablets were shown in **Figure 1**. Maximum controlled release of the drug was observed in F5 (40:60); It released 78.95±1.48 % for 24 h. The drug release followed by zero order profile (R^2= 0.9885). But as the concentration of HPMC increases beyond 60%, the matrices form rigid gel structure which hampers the release of the drug. The maximum controlled release of formulation (F5) is attributed due to its greater swelling of matrices.

Formulations of Starch: Carbopol 934 (E1 to E6)

Controlled release tablets were fabricated with Starch: Carbopol 934 in the ratio of 85:15, 75:25, 60:40, 50:50, 40:60 and 25:75. Release profile of single layered tablets was shown in the **Figure 2**. Maximum controlled release was observed in F4 and F5. By using 50% of Carbopol 934 it released 79.09±1.67% and 76.33 ± 1.98% respectively. This showed that as the concentration of Carbopol 934 increases upto 50% the release rate of formulation also increases but beyond that it did not show proper controlled release.

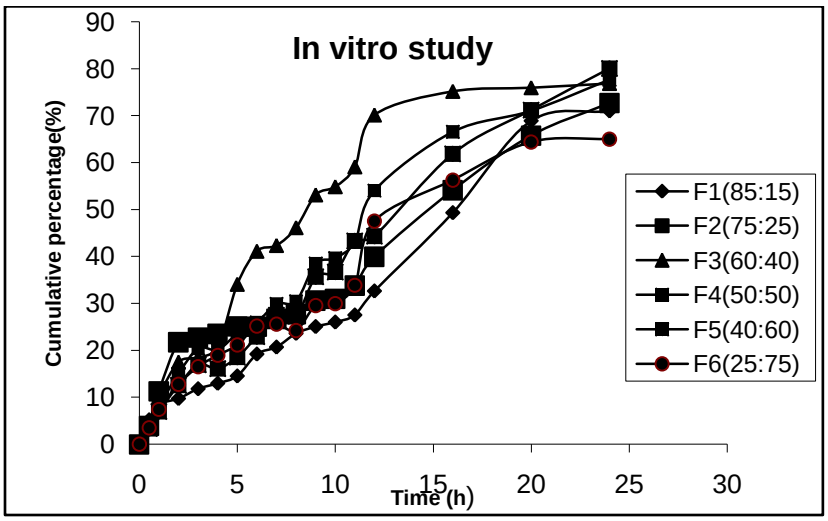

Figure 1.Formulations of Starch: HPMCK15M tablets (F1 to F6)

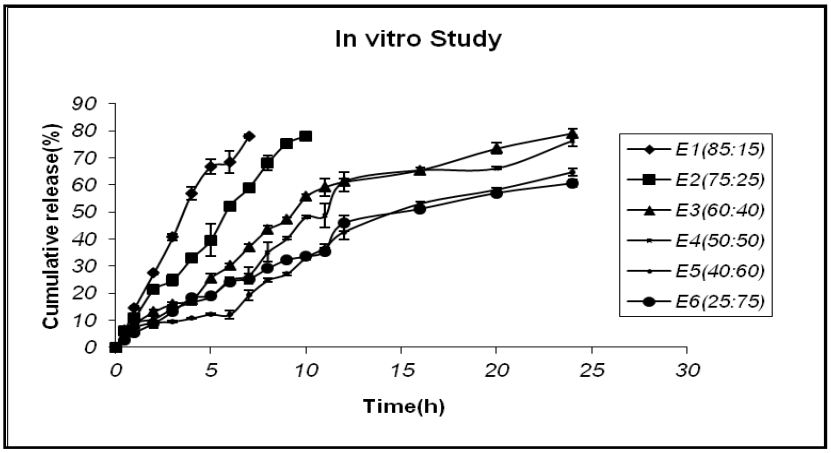

Figure 2. Formulations of Starch: Carbopol 934 tablets (F1 to F6)

The possible reason behind that there might be ionization of Carbopol 934 at experimental pH 6.8 at higher concentration and this ionization process will lead to development of negative charge at polymer surface and it changed into an extended structure allowing water molecule to penetrate into it which leads to higher swelling and other reason may be the mixing of starch and Carbopol 934 within the particle resulting in a reduction of carboxylic groups available for hydration as a part of those acid groups situated in the inner core of the particle and as a part interacted with the hydroxyl groups of starch. Due to higher mobility of the hydrated polymer chain of the individual Carbopol 934 particles in the physical mixtures, a more extensively swollen network which leads to diffusion of drug in controlled manner. Data of the in vitro release was fit into different equations and kinetic models used were zero order equation, first order equation, Higuchi and Korsemeyer-peppas models. Formulation E4 followed Higuchi equation (R^2=0.9594). Therefore, according to all the previous studies, F5 and E4 are selected further for in vivo study.

In vivo study

The plasma concentration profile for bioadhesive tablets in rabbits was measured and shown in Table. Plasma concentration profile of formulated tablets of starch and HPMC (F5) is shown in **Figure 3.** The t_{max} was observed to be 16h for buccal tablets (F5) as compared to 4h for oral tablets. After administration of Carvedilol oral conventional tablet (carca 6.25mg), rapid absorption was observed. t_{max} of formulated tablets of Starch:HPMCK15M (F5) showed slow absorption in 16h. But it was controlled upto 24h, which was seen by plasma concentration profile.

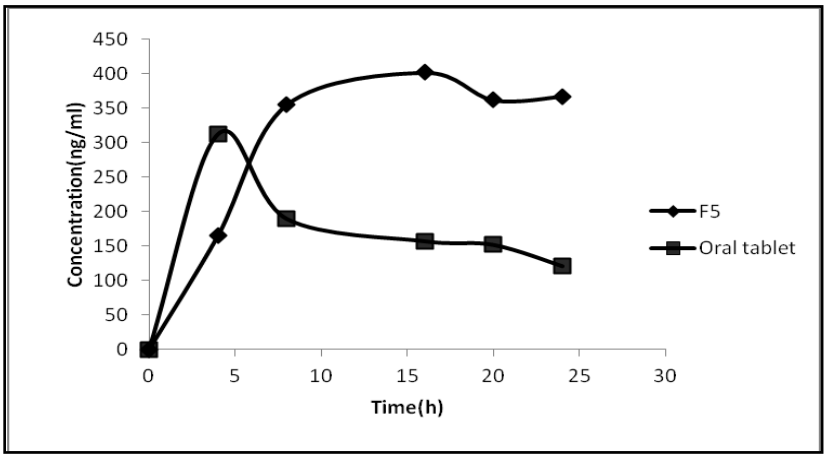

Figure 3.Plasma concentration Vs Time profile for F5 and oral conventional tablets

The C_{max} values were observed higher (419.16 ± 26.05 ng/ml) for Carvedilol buccal tablets (F5) as then compared to oral tablets (334.2±25.95 ng/ml). The AUC values of buccal administration of tablets (7057.3 ± 419.32 ng/ml) were significantly higher than the oral administration of tablet (4523.6 ± 202.6 ng/ml) which revealed the increase in bioavailability of coupled with controlled release of Carvedilol by formulated tablets of starch and HPMC (F5).

The plasma concentration profile of formulated tablets of starch and Carbopol 934 (E4) was shown in **Figure 4**. The t_{max} was observed to be 20h for buccal tablets (F16) as compared to 4h for oral conventional tablet .Formulated tablets of Starch: C934 (E4) showed slow absorption initially after which gave the controlled release of drug. The C_{max} values observed were higher (535.25± 12.75 ng/ml) for Carvedilol buccal tablet (E4) than oral tablets (334.2±25.95 ng/ml) which is slightly higher than $C_{max}$of oral conventional tablet. The AUC values after buccal administration of tablets (9204.217 ± 200.44 ng/ml) were significantly higher than those observed after oral administration of tablet. But, it shows C_{max} and AUC higher as compared to formulated tablets of Starch: HPMC (F5).

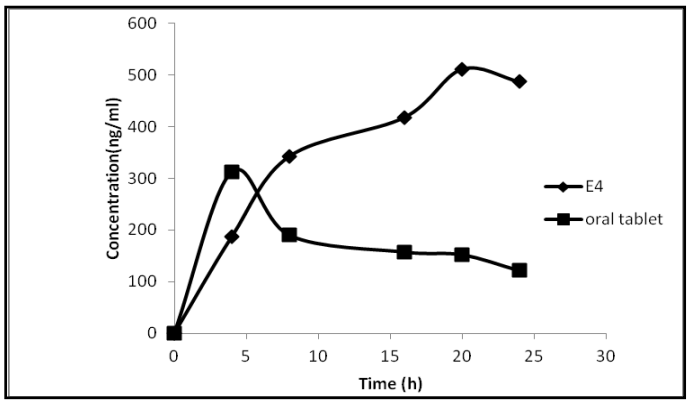

Figure 4. Plasma concentration Vs Time profile for E4 and oral conventional tablets.

CONCLUSIONS

It can be concluded that plasma profile of all the formulated tablets showed that bioavailability increased as compared with oral conventional tablets of Carvedilol available in market. However, formulation containing starch and Carbopol 934(E4) showed better bioavailability as compared to tablet containing Starch and HPMCK15 (F5) and The bioadhesive strength of the formulations containing polymers were in the order of E4> F5.Further work is needed to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic studies on human beings.

ACKNOWLEDGEMENT

The authors are grateful to the SPTM, NMIMS University (Mumbai) for providing the necessary infrastructures.

REFERENCES

1. Vamshi V, Chandrasekhar K, Rao M. Development of mucoadhesive patches for buccal administration of Carvedilol. Current Drug Delivery 2007; 4:27-39.
2. Kulkarni U. Desai S. Design and development of felodipine buccal mucoadhesive patches. Int J Current Pharm Res 2010; 2:3.
3. Balamurugan M, Saravanan V, Ganesh P. Development and In-vitro evaluation of muco adhesive buccal tablets of Domperidone. Res J PharmTech 2008; 1:4.
4. Ahuja, A, Khar RK. Mucoadhesive drug delivery systems. Drug Dev Ind Phar 1997; 23(5):489:515.
5. Jimenz MR, Zia H, Rhodes CT. Assessment of an in-vitro method of measuring the bioadhesive of tablets. Int J Pharm1993; 89:223-228.

6. IegglI C, Cardose SG, Belle LP. Validation of UV-Spectrophotometric and nonaqueous titration methods for the determination of Carvedilol in pharmaceutical formulation. J AOAC Int 2005; 5:1299-303.
7. Spiegeleer BP, VanVooren L, Voorspoiels J. Dissolution stability and IVIVC investigation of a buccal tablets. Analytic Chemical Acta 2001; 446:345-351.
8. Smart, JD. Some formulation factor influencing the rate of drug release from bioadhesive matrices. Drug Dev Ind Pharm 1992; 18:223-234.
9. Attala MA, Shaltout SE. Transbuccal permeation, anti-inflammatory activity and clinical efficacy of piroxicam formulated in different gels. Int J Pharm 2004; 276:11-28.
10. Metia PK, Bandyopadhyay. Abstract: In vitro and in vivo evaluation of novel mucoadhesive buccal oxytocin tablets prepared with dileniaindica fruit mucilage. Pharmazie 63:270-274.
11. Wang L, Tang X. A Novel Ketoconozole bioadhesive effervescent tablet for vaginal delivery and in vitro and in-vivo evaluation. Int J Pharm 2008; 350:181-187.
12. Kumar M, Kuriachan MA. Bioadhesive pH of micro particles for oral delivery of insulin. Trends. Biomater Artif Crams2005; 18:2.
13. Minghetti P, Colombo A, Montanari L. Mucoadhesive slow tablets of acretin: design and in vivo evaluation. Int J Pharmaceutics.1998; 169:195-205.