ISSN: 2395-0536

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF LOCASAMIDE

M.V. Phanideep*, Shaik.Harun Rasheed, P.Shanmukhi

*Department of Pharmaceutics DCRM College of Pharmacy, Inkollu, Prakasam District -523167, Andhra Pradesh, India.

ABSTRACT

Epilepsy is the most common neurological disorder results in excessive electrical activity in part or all of the brain resulting in recurrent seizures. Lacosamide (LCM) is a new antiepileptic drug approved by US-FDA for the treatment of partial onset seizures. It acts in a new way that it has two novel mechanisms of action which differs from other existing anti epileptic drugs. Lacosamide has less severe side effects and less drug interactions with other drugs. HPMC, pvp, Hypromellose, PEG 6000,MCC,Lacosamide, Magnesium sterate, Talc, and were evaluated for physico-chemical parameters i.e; drug content, swelling index, dissolution studies. All the formulations showed compliance with pharmacopeia standards. Based on the evaluation results,F3 formulations were selected as the best formulations and were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation.

Key words: Lacosamide**,** oral controlled release formulation, controlled release.

Author for correspondence:
M.V Phanideep,
Department of Pharmaceutical Analysis,
Chalapathi Institute of Pharmaceutical Sciences,
Lam, Guntur-522034, Andhra Pradesh, India.

Email: phanibethemost@gmail.com.

INTRODUCTION

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration the drug is due to the well absorbed into the food stuff ingested daily (1).

Sustained release (S.R)/ Controlled release (C.R) pharmaceutical products have gradually gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized (2). Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastrointestinal disturbances.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (3).

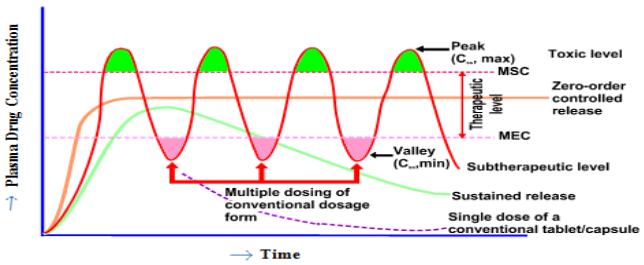


Fig-1 A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

As can be seen in the graph (Fig-1), administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms like solution, suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (4).

Controlled Release Drug Delivery Systems (CRDDS)

- More precisely, controlled delivery can be defined as
- Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
- Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

Potential Advantages of Controlled Drug Therapy

- Patient compliance due to reduction in the frequency of designing.
- Employ minimum drug.
- Minimize or eliminates local and systemic side effects.

Disadvantages of Controlled Drug Therapy

- They are costly.
- Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.

Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action (5).

Classification of Oral Controlled Release System

A) Diffusion Controlled Systems
I. Reservoir Devices
II. Matrix Devices
B) Dissolution controlled system
I. Matrix Dissolution Controlled System
II. Encapsulation Dissolution Controlled system
C) Diffusion and Dissolution Controlled System.

Factors Influencing the Design and Performance of Controlled Release Products

The type of delivery system and route of administration of the drug presented in controlled drug delivery system may depend upon two properties (6). They are

- Physicochemical Properties of drugs
- Biological Factors.

1. Physicochemical Properties of drugs

1. Dose size
2. Ionization, P^{Ka} & Aqueous Solubility
3. Molecular size and diffusivity
4. Partition coefficient
5. Drug Stability
6. Protein Binding

II. Biological Factors

1. Biological Half-Life
2. Absorption, Metabolism

Monolithic Matrix System

In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute throughout the matrix core of the release retardant. Alternatively, drug-release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wet granulation or beads (7).

To characterize and define the matrix systems the following properties of the matrix are considered.

1. Chemical nature of the support.
2. The routes of administration.
3. The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).
4. The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).

The classification of the matrix-based systems is based on the following criteria.

- Matrix structure
- Release kinetics
- Controlled release properties (diffusion, erosion and swelling).
- Chemical nature and the properties of the applied release retardant(s).

Drug Release Kinetics -Model Fitting of the Dissolution Data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, tor Q=f (t). Some analytical definitions of the Q (t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer-Peppas models. (8-12).

Zero Order Kinetics

Kinetic equation for Zero order release is as follows

$$Q_1 = Q_0 + K_0 t$$

Where $Q_1$is the amount of drug dissolved in time *t*, $Q_0$is the initial amount of drug in the solution (most times, Q_0=0) and $K_0$is the zero order release constant.

$$f_t = K_0 t$$

Where f_t = 1-(W_t/W_0) and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction

versus time will be linear if the previously established conditions were fulfilled drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First Order Kinetics

Kinetic equation for the first order release is as follows

$$Log\ Q_t = log\ Q_0 + K_1t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphical representation of the decimal logarithm of the released amount of drug versus time will be linear.

Higuchi Model

ft = KH t1/2

Where K_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent.

Hixson–Crowell model

Hixson and Crowell (13) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

MATERIALS

LACOSAMIDE, HPMC, PEG 6000, MCC, PVP, Magnesium Stearate, Talc.

METHODS

Construction of Standard Graph of Lacosamide

Accurately weighed amount of 100 mg of Lacosamide was transferred into a 100 ml volumetric flask. Methanol was added to dissolve the drug and the primary stock solution was made by adding 100 ml of methanol. This gives a solution having concentration of 1 mg/ml of Lacosamide stock solution. From this primary stock 10 ml was transferred in to another volumetric flask and made up to 100 ml with 6.8 pH phosphate buffer and this gives secondary stock solution. From this secondary stock 0.2, 0.4,0.6, 0.8 and 1.0 ml, was taken separately and made up to 10 ml with 6.8 pH phosphate buffer to produce 2, 4, 6, 8 and 10 µg/ ml respectively. The absorbance was measured at 250 nm using a UV spectrophotometer (Systronic, Hyderabad, India).

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 ml of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200ml volumetric flask and 22.4 ml of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.

Preparation of Lacosamide Matrix Tablets

All the matrix tablets, each containing 100 mg of Lacosamide, were prepared by direct compression method and also to study the effect of various ratios of different types of polymers on the drug release.

Melt granulation method

Melt the PEG 6000 in a china dish at 55-65°C and add drug. Slowly add the polymer mixture & filler with spatula (Tumbling method) then stir well scrap until it reaches to Room temperature Pass through 22 No.

mesh and the through 44 no sieve to separate the granules and fines. Finally add talc and magnesium stearate to the granules (14-15).

Formulations

In formulations prepared, the release retardants included were Carbopol934p, PolyethyleGlycol(PEG6000), Hydroxy propyl methylcellulose (HPMCK4M). Microcrystalline cellulose (MCC) was used as diluents. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. Compositions of different formulations were given in the Table-1.

Table-1 Composition of Matrix Tablets Containing Carbopol 934P

Ingredients	Formulation code (mg/tab)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lacosamide	100	100	100	100	100	100	100	100	100
PEG 6000	60	80	100	60	80	100	60	80	100
HPMC K4 M	100	120	140	120	140	100	140	100	120
MCC	130	90	50	90	50	130	50	130	90
PVP K 30	5	5	5	5	5	5	5	5	5
Ma.stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3

EVALUATION OF FORMULATION (TABLETS)

Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 250 mg tablets and none by more than double that percentage (Table-4).

Dissolution Study

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 ± 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 10 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 250 nm (Table-5)

Fourier Transform Infrared Spectroscopy (FTIR) Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}

RESULTS AND DISCUSSION

Calibration Curve of Lacosamide in 6.8pH:

Standard graph of Lacosamide was constructed using 6.8 pH phosphate buffer. Various concentrations 2 to 10 µg/mL were prepared. The absorbance of prepared concentrations was measured at 254(6.8 pH) nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented (Table-2, 3 and Fig-2, 3).

Table-2 Standard values of Lacosamide

Concentration (µg/ml)	absorbance
2	0.15
4	0.33
6	0.49
8	0.68
10	0.89

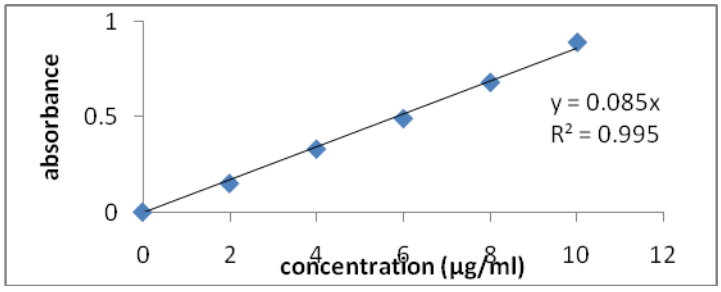
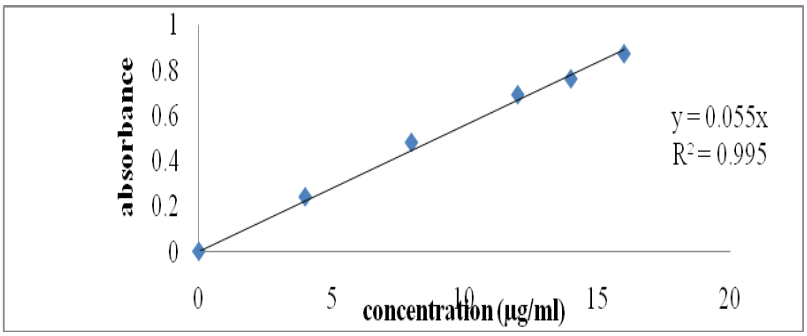


Fig-2 Standard calibration curve of Lacosamide

Table-3 Values of Calibration curve in 0.1N HCl



Concentration (µg/ml)	Absorbance
4	0.24
8	0.48
12	0.69
14	0.76
16	0.87

Fig-3 Standard calibration curve of HCL

FT-IR STUDIES

The FTIR spectra of the drug (alone), polymer (alone) and the drug-polymer (mixture) were recorded by the potassium bromide pellet method. From the infrared spectra it is clearly evident that there were no drug-polymer interactions of the drug (Fig-4 and 5).

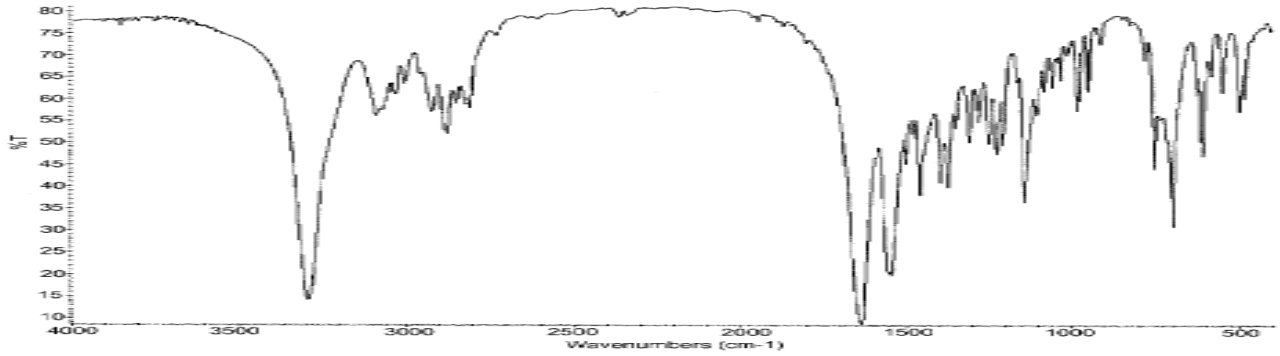


Fig-4 FT IR of Lacosamide

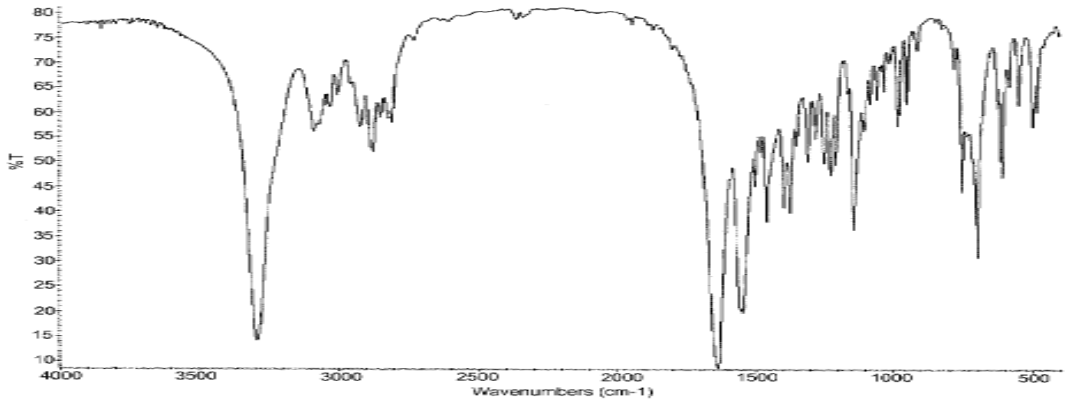


Fig-5 FT-IR Spectra of Lacosamide final formulation

Table-4 Average weight variation

Formulation Code	Weight Variation(mg)
F1	399.6
F2	398.75
F3	401.67
F4	396.40
F5	402.56
F6	399.67
F7	397.40
F8	400.89
F9	401.7

Table-5 Dissolution Profiles of Formulations: *in vitro* release profile

Time (hr)	% drug release								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	9.7	10.5	15.6	18.5	15.5	10.5	9.6	21.2	15.6
4	15.6	15.8	28.5	24.6	21.6	15.6	15.7	35.4	24.5
6	25.5	26.9	36.7	35.6	30.5	28.5	22.9	46.7	28.9
8	38.9	49.8	58.5	41.7	39.5	39.6	35.6	58.9	45.6
10	65.8	70.2	78.28	60.7	51.8	54.6	43.2	67.9	58.9
12	79.8	85.4	97.8	78.9	70.9	68.9	55.2	81.5	69.8

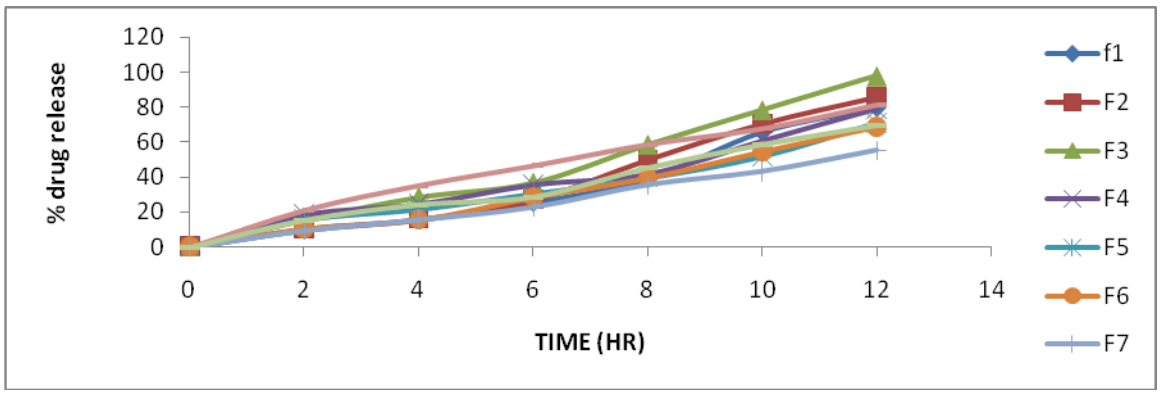


Fig- 6 Dissolution profile of Lacosamide Matrix Tablets

CONCLUSION

Success of the Inventor drug release studies recommends the product for further in vivo studies, which may improve patient compliance. From the results, formulationF3 containing Lacosamide 100 mg, PEG6000 100 mg and HPMC K4M 140 mg evolved as the optimized formulation and it releases more than 98.7% drug in 12hrs. IR spectroscopic studies indicated that there are no drug-excipient interactions in the optimized formulation. The optimized formulation F3 can be considered as a promising Sustained drug delivery system of Lacosamide providing nearly zero order drug release over a period of 12 hrs (Fig-6).

REFERENCES

1. Beckett AH, Stenlake JB. Practical Pharmaceutical Chemistry. 4th ed. CBS Publisher and Distributors, Delhi, 1997.
2. Sethi PD. Quantitative Analysis of Drugs in Pharmaceutical Formulation, 3rded., CBS Publisher and Distributors, Delhi, 1998.
3. Sethi PD. High Performance Liquid Chromatography, CBS Publisher and Distributors, Delhi,1998.
4. Higuchi T, Brochman E, Hanseen H. Pharmaceutical Analysis, CBS Publisher and Distributors, Delhi, 2005.
5. Mendham J, Denney RC, Barnes JD, Thomas MJ. Vogel's text Book of Quantitative Chemical Analysis, 6thed. Pearson education Pvt Ltd, 2002.
6. The Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Published by The India.
7. Anderson NR *et al*. Quantitative evaluation of pharmaceutical effervescent systems I: design of testing apparatus. *Pharm Sci* 1982; 71: 3–6.
8. Barra J, Somma R. Influence of the physicochemical variability of magnesium stearate on its lubricant properties: possible solutions. *Drug Dev Ind Pharm* 1996; 22: 1105–1120.
9. Billany MR, Richards JH. Batch variation of magnesium stearate and its effect on the dissolution rate of salicylic acid from solid dosage forms. *Drug Dev Ind Pharm* 1982; 8: 497–511.
10. Bos CE *et al*. Lubricant sensitivity in relation to bulk density for granulations based on starch or cellulose. *Int J Pharm* 1991; 67: 39–49.
11. Bracconi P *et al*. Structural properties of magnesium stearate pseudopolymorphs: effect of temperature. *Int J Pharm* 2003; 262:109–124.
12. Brittain HG. Raw materials. *Drug Dev Ind Pharm* 1997; 15: 2083–2103.
13. Dansereau R., Peck GE. The effect of the variability in the physical and chemical properties of magnesium stearate on the properties of compressed tablets. *Drug Dev Ind Pharm* 1987; 13: 975–999.
14. Desai DS *et al*. Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. *Int J Pharm* 1993; 91: 217–226.
15. Ebba F *et al*. Stress relaxation studies of granules as a function of differentlubricants. *Eur J Pharm Biopharm* 2001; 52: 211–220.