International Journal of Drug Development & Research
| January-March 2012 | Vol. 4 | Issue 1 | ISSN 0975-9344 |
Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03,& H index 2

FULL Length Research Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Development and Characterization of Novel Pharmaceutical Crystalline Complex of Lomefloxacin

Veerendra K. Nanjwade[1*], F. V. Manvi[1], Shamrez Ali. M[2], Meenaxi M. Maste[1], Basavaraj K. Nanjwade[1]

[1*] Department of Pharmaceutics, KLE University College of Pharmacy, JN Medical College Campus, Belgaum – 590010, Karnataka, India.

[2]Simpex Pharma Pvt. Ltd, Sigaadi, Kotdwara – 246149. District Pauri Garhwal Uttarakhand,

Abstract

The objectives of this study were to prepare and characterize the novel Lomefloxacin-Salicylic acid and Lomefloxacin-Urea to demonstrate the enhanced dissolution of Lomefloxacin by co crystal formation in comparison with the pure drug. Lomefloxacin-Salicylic acid and Lomefloxacin-Urea co crystal was prepared using greener technique cogriding with aim of enhancing their dissolution rate sand their bioavailability. DSC, IR and PXRD were used to characterize the novel solid form. The dissolution and chemical stability were assessed and compared with marketed Maxaquin. Pharmaceutical co crystals are new solid forms with physicochemical properties that appear promising for drug product development. Novel solid co crystals with distinct melting. DSC, FTIR and PXRD data was obtained. The co crystal of lomefloxacin with salicylic acid (SA) has been shown to have higher solubility than lomefloxacin. In this study, we aimed to characterize the pure drug and the co crystals with the salicylic acid and urea. Remarkably, two new co crystals of lomefloxacin were discovered in this study. The study indicates that the improved aqueous solubility of the co crystals leads to improved dissolution of Lomefloxacin. Thus, the co crystals are a viable alternative solid form that can improve the dissolution rate and bioavailability of poorly soluble drugs. Subsequently, differential scanning calorimetry was used to investigate the co crystal formation. The formation of co crystals was also verified using liquid-assisted grinding. The spectral patterns of lomefloxacin, salicylic acid and the complex were different. The physicochemical properties such as solubility and dissolution rate of this complex will be further investigated.

*Corresponding author, Mailing address:
Veerendra K. Nanjwade
Department of Pharmaceutics
KLE University College of Pharmacy
JN Medical College Campus
BELGAUm-590010, Karnatak, India
Cell No: 0091 9738173632
E-mail: vknanjwade@gmail.com

Key words:
Lomefloxacin, dissolution rates, cocrystals, product development

How to Cite this Paper:
Veerendra K Nanjwade "Development and Characterization of Novel Pharmaceutical Crystalline Complex of Lomefloxacin", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 227-233

Article History:----------
Date of Submission: 27-01-2012
Date of Acceptance: 11-04-2012
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

Improvement of API physicochemical and biopharmaceutical properties as well as in vivo performance and, hence, are a potential new alternative in the selection of optimal solid forms in drug product development[1, 2]. Traditionally, co-

crystal screening has been based on empirical methods such as solvent evaporation, crystallization from melts, and grinding[3, 6].

The improvement of the physicochemical properties of active pharmaceutical ingredients (APIs) has become a major concern in the pharmaceutical industry. Both branded and generic pharmaceutical companies spend considerable efforts and resources on the discovery of new crystalline forms of their APIs. This intense research has been driven by the need for improving undesirable properties of APIs witnessed in the commercialization pipelines[7, 8].

APIs are complex chemical structures with functional groups that may take part in the molecular recognition events. It is the presence of these functional groups, such as amides and carboxylic acids that provides inability to engage in supramolecular event with the co crystal formers that show complementary hydrogen bond donor and acceptorsites[8].

Pharmaceutical co crystals, a recent addition to the class of crystalline solids, are generating increasing interest, and offer an alternative means of improving the physicochemical properties

of an API[9-11]. Cocrystallisation offers several key advantages: (1) co crystals are crystalline with definite stoichiometry, leading to better solid-state stability and more predictable physical properties and performance than amorphous solids; (2) co crystal design involves altering hydrogen bonding motifs rather than making or breaking covalent bonds, thus retaining the safety and pharmacological profiles of the drug molecule; (3) co crystals of all types of APIs(weakly acidic or basic or non-ionisable) can in principle be prepared, in contrast to salt formation technology; (4) greater diversity is possible with co crystal solid forms because of the availability of numerous coformers (food additives, preservatives, pharmaceutical excipients, and other APIs); (5) co crystals offer patenting opportunities because they are new solid forms of APIs; (6) co crystals can be generated using green production technologies such as grinding.

Lomefloxacin HCL is a bactericidal fluoroquinolone agent with activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of lomefloxacin HCl results from interference with the activity of the bacterial enzymes DNA gyrase and topoisomerase IV, which are needed for the transcription and replication of bacterial DNA. The elimination half-life was approximately 8 hours. There was no drug accumulation with single-daily dosing in patients with normal renal function.

Pharmaceutical co crystals can be prepared by several methods such as mechanochemical or traditional solution crystallization methods approaches. The uses of reaction crystallization methods, thermal microscopy and differential scanning calorimetric methods have also been reported. The mechanochemical methods such as grinding may be ideal for co crystal screening.

Grinding and solution crystallization methods are widely used for co crystal screening purpose. These methods differ primarily by the amount of liquid used and means to convert a given amount of starting components into crystals[12-13].

The API under consideration in the current work is Lomefloxacin HCl no published reports on the crystal structure and solid state characterization of solid not reported.

MATERIALS AND METHODS

Materials:

Lomefloxacin HCl was received as a gift sample from the Simpex Pharma Pvt. Ltd., Uttarakhand, India. Other chemicals and solvents were obtained from different commercial suppliers.

Preparation of Lomefloxacin -Salicylic acid co crystals:

Lomefloxacin-salicylic acids were prepared at various molar ratios by kneading method using motar and pestle for 30 min to obtain the co crystals.

Preliminary Characterization:

The melting point of samples was determined by melting point apparatus.

Fourier transforms infrared spectroscopy:

Infrared spectra of the pure lomefloxacin HCl, Lome-SA and Lome-Urea were recorded using a IR 230 spectrophotometer (Shimadzu). In the range of 650-4000cm^{-1}with KBr pellets.

Differential scanning calorimetry:

Thermal analysis of the samples was performed on a DSC Q1000 (TA Instruments) which was calibrated for temperature and enthalpy using indium. Samples (3-5 mg) were crimped in non-hermetic aluminum pans and scanned from 30 to 200 ^{o}C at a heating rate of 10^{o}C/min under a continuously purged dry nitrogen atmosphere (flow rate 50mL/min).The instrument was equipped with a refrigerated cooling system. The data were collected in triplicate for each sample.

Powder X-ray diffraction:

The solid phases obtained from the stability and solubility experiments were analyzed by PXRD, and the resulting diffraction patterns were compared with the diffraction patterns of pure phases. The patterns were collected ona Siemens DIFFRAC plus 5000 powder diffractometer with CuKradiation (1.54056 A°). The tube voltage and amperage were set at40 kV and 40mA, respectively. The divergence slit and anti-scattering slit settings were variable for illumination on the 20 mm area on the sample. Each sample was scanned with2θ between 5^{o}and 60 ^{o}with a step size of 0.02 ^{o} and 0.5 s at each step. The sample stage was spunat 30 rpm. The instrument was precalibrated using a silicon standard.

RESULTS AND DISCUSSION

In the present study, the co grinding method was used to prepare the co crystal because mechanochemical technology was shown to be available to the pharmaceutical field and be friendlier to the environment than the solvent method. When there was LomefloxacinHCl co grinding with the salicylic acid at a molar ratio of 1:1 for 30 min, In addition to salicylic acid, the co crystal formation of Lomefloxacin HCl with other carboxylic acids such as maleic acid, glutaric acid and malonic acid was investigated.

The physicochemical properties of Lomefloxacin HCl, salicylic acid, urea at a molar ratio of 1:1 were investigated by other solid state analytical methods. The molecular interaction between lomefloxacin HCl and salicylic acid was examined by FTIR spectroscopy. All the spectra of the lomefloxacin HCl and its co crystals with urea, salicylic acid and oxalic acid are depicted in (Fig.2, 3, 4, 5.).

Co crystalline phase characterization and identification of cocrystalstudied using differential scanning calorimetry (DSC). DSC data is presented for the lomefloxacin HCl and its co crystals with urea, salicylic acid and oxalic acid only (Figs.6, 7, 8, 9) and powder X-ray diffraction (PXRD). PXRD data is presented for the lomefloxacin HCl and its co crystals with urea, salicylic acid and oxalic acid only(Fig.10, 11, 12, 13).

The standard curve of lomefloxacin HCl in methanol (Table 3 and Figure 1), it was observed that the drug obeys beer Lambert's law in concentration range 1-5µg/ml.

The melting point of the obtained drug sample was found to be 285^{o}C, which is within the reported value of 290- 300^{o}C. It complies with official standards thus indicating the purity of the drug sample (Table 2).

Lomefloxacin HCl was analyzed by FTIR spectral analysis for identification of the pure drug. From the spectra, it was concluded that there was no

interference in the functional group as the principal peaks of the lomefloxacin HCl were found to be unaltered. The FTIR spectrum of lomefloxacin HCl and in combination with the urea, salicylic acid and oxalic acid is shown in Figure 2, 3, 4 and 5.Differential Scanning Calorimetry (DSC) can be used to investigate and predict the changes in crystalline form of the drug. Polymorphism is the capability of a substance to crystallize into two or more different crystalline forms. Any crystalline changes in the drug may change its melting point, bioavailability, and drug release kinetics. The crystalline change in the drug lomefloxacin HCl was studied using differential scanning calorimetry (DSC) by testing the melting characteristics of the drug. Figure 6, 7, 8 and 9compares the DSC thermo gram of lomefloxacin HCl and its mixture with urea, salicylic acid and oxalic acid.

Preliminary characterization of 1:1 and 1:2 Co crystals:

The DSC thermograms and pXRD analysis strongly suggests the formation of a new co crystalline form. Our current efforts in generating pure co crystals of this new phase and a follow-up single crystal X-ray study should confirm this true nature of this physicochemical.

The physicochemical properties of lomefloxacin HCl, urea, salicylic acid and oxalic acid at a molar ratio of 1:1 were investigated by other solid state.

CONCLUSIONS

Co crystals of API were produced using co grinding method and a new co crystalline form of LOME-SA was unveiled. GRIND method revealed to be a suitable method. This study demonstrates the ability of producing co crystals of several APIs, confirming the potential of co grindings as alternative methods to produce pharmaceutical co crystals. Further work is currently in progress towards a thorough characterization of this new LOME-SA co crystal and analysis of its physicochemical properties. The physicochemical properties such as solubility and dissolution rate of this complex will be further investigated. An extensive study about the control of co crystal stoichiometry using novel SCF and Spray drying techniques with kinetic and thermodynamic aspects of co crystals formation will be addressed in a future work.

ACKNOWLEDGEMENT

We are very grateful to the vice-chancellor and registrar of KLE University and also would like to thank all staff of KLE university college of Pharmacy, Belgaum for providing constant support and enthusiasm to carry out this work.

Table 1: Identification of drug

Identification test	Result of sample obtained	Reported standards
Appearance	Solid	Solid
Color	Pale yellow	Pale yellow
Odor	Odorless	Odorless

Table 2: Melting point

Reported	Observed
Above 285°C	290- 300°C

Table 3: Standard curve in Methanol

Sl. No	Conc. mcg/ml	Peak area
1	0	0.00
2	1	0.175
3	2	0.317
4	3	0.478
5	4	0.644
6	5	0.802

Figure 1: Calibration curve of Lomefloxacin HCl in Methanol

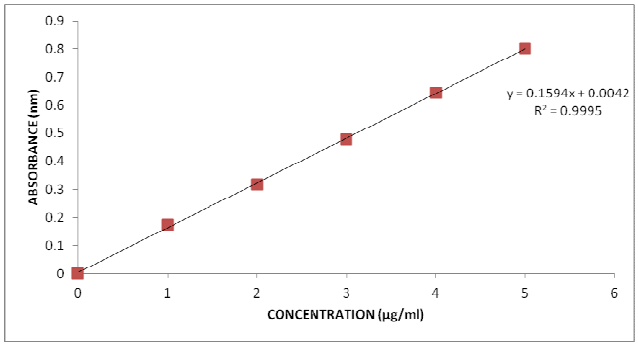


Fig. 2: IR spectra Of Lomefloxacin HCl

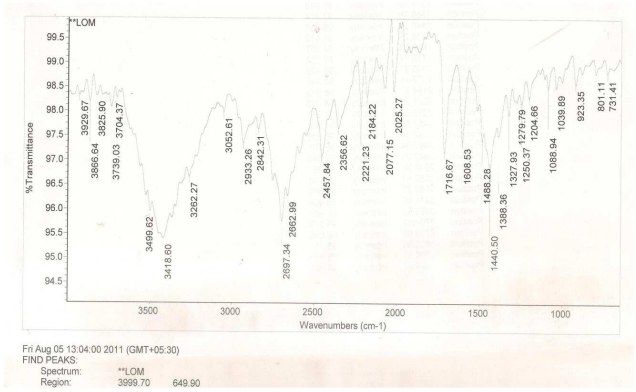


Fig. 3: IR spectra Of Lomefloxacin HCl + Urea

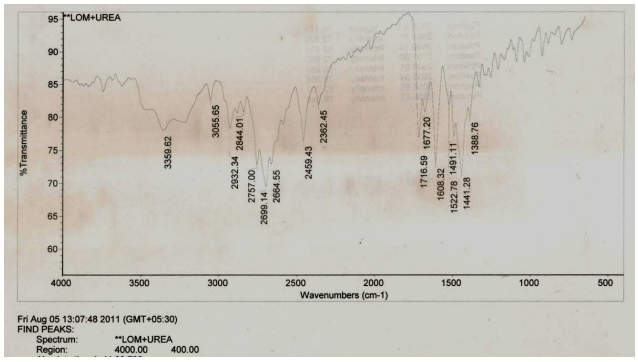


Fig. 4: IR spectra Of Lomefloxacin HCl + Salicylic acid

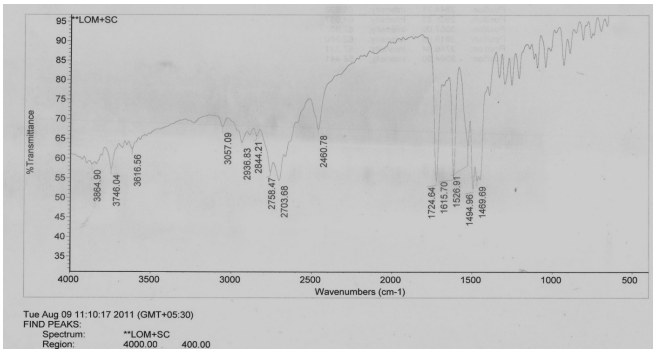


Fig. 5: IR Spectra of Lomefloxacin HCl + Oxalic acid

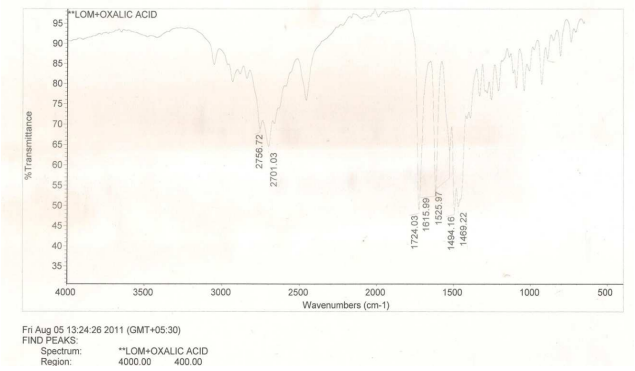


Fig. 6: DSC of Lomefloxacin HCl.

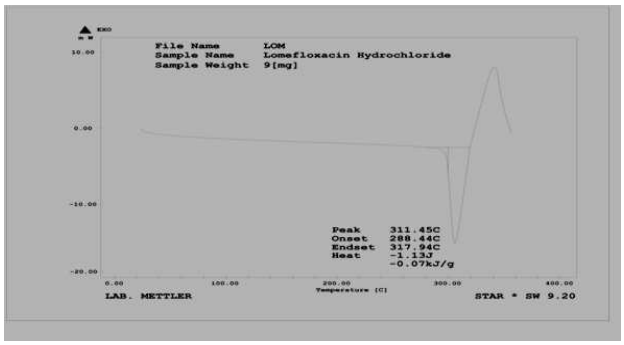


Fig. 7: DSC of Lomefloxacin HCl and Urea.

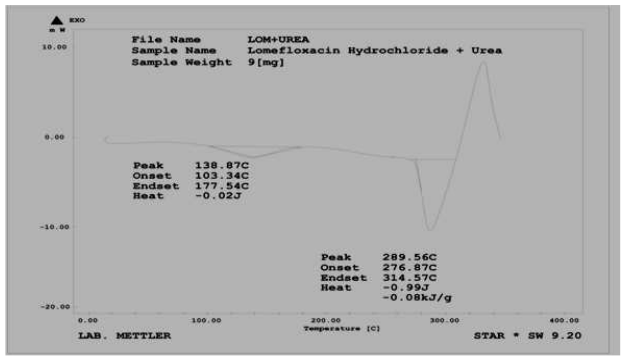


Fig. 8: DSC of Lomefloxacin HCl and Salicylic acid.

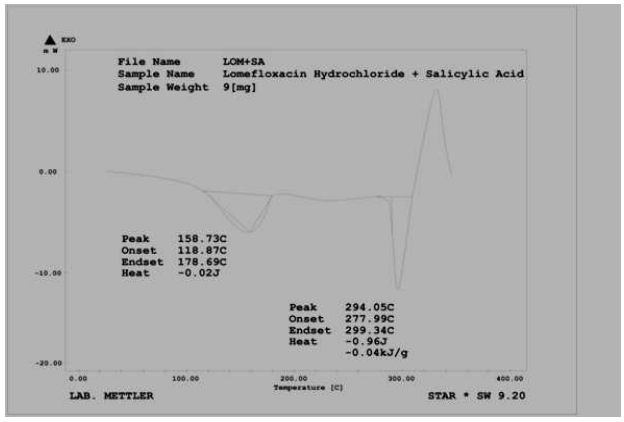


Fig. 9: DSC of Lomefloxacin HCl and Oxalic acid.

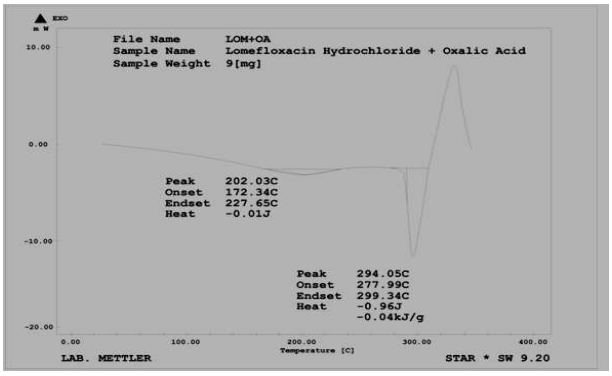


Fig.10: p-XRD of LomefloxacinHCl

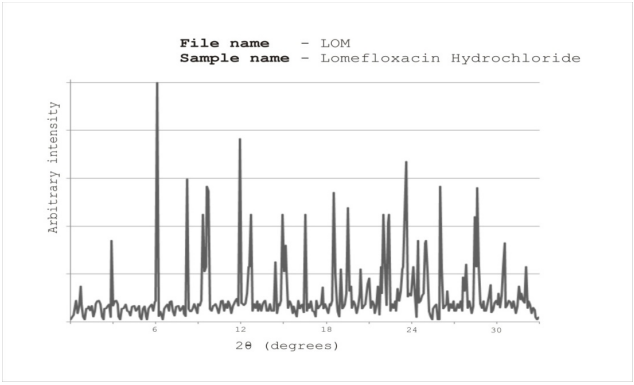


Fig.11: p-XRD of Lomefloxacin HCl and Urea.

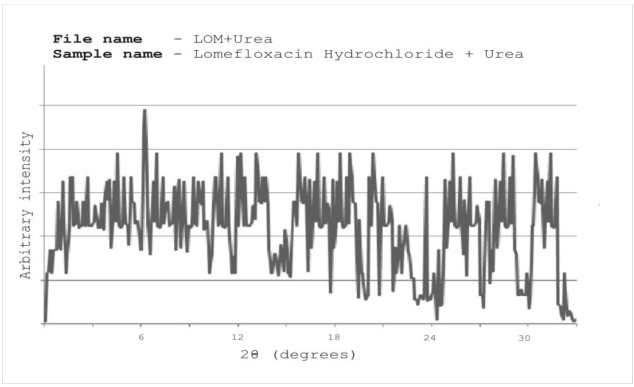


Fig.12: p-XRD of Lomefloxacin HCl and Salicylic acid.

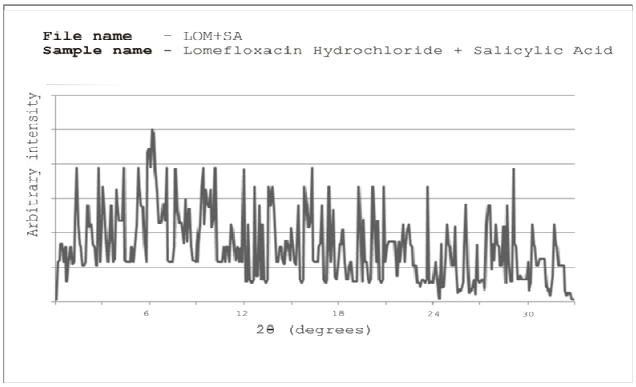
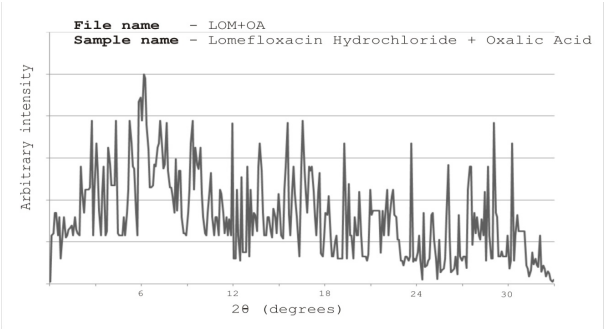


Fig.13: p-XRD of LomefloxacinHCl and Oxalic acid.



REFERENCES

1) Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties.Cryst. Growth Des 2009; 9(6): 2950-2967.

2) Jung MS *et al.* Bioavailability of indomethacin-saccharin cocrystals.J Pharm Pharmacol2010; 62(11): 1560-1568.

3) Vishweshwar P *et al.* Pharmaceutical co-crystals.J Pharm Sci 2006; 95(3): 499-516.

4) Trask AV, Jones W. Crystal engineering of organic cocrystals by the solid-state grinding approach. Top CurrChem 2005; 41–70.

5) Berry D, Seaton C, Clegg W, Harrington R, Coles S, Horton P, Hursthouse M, Storey R, Jones W, Friscic T.Cryst. Growth Des. 2008; (8), 1697–1712.

6) Basavoju S *et al.*Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization.Pharm Res 2008; 25(3): 530-541.

7) BrittainH. Polymorphism in Pharmaceutical Solids.New York: Marcel Dekker, Inc., 1999.

8) ThayerAM. Form and function. ChemEng News2007; 85(25): 17-30.

9) Vishweshwar P *et al.* Pharmaceutical co-crystals. J Pharm Sci2006; (95): 499-516.

10) Jones W *et al.* Pharmaceutical cocrystals: an emerging approachto physical property enhancement. MRS Bull2006; 31: 875-879.

11) Schultheiss N, Newman A. Pharmaceutical cocrystals and theirphysicochemical properties. Cryst Growth Des2009; 9(6): 2950-2967.

12) Trask AV, Jones W. Achievingpolymorphic and stoichiometric diversity in cocrysatal formation: importance of solid state grinding, powder x-ray structure determination seeding, Cryst.Growth Des. 9(20009) 1106-1123.

13) Vishweshwar P *et al*. Synthesis and structural characterization of cocrystal and pharmaceutical cocrystals: mechanochemitstry vs. slow evaporation from solutionCryst. Growth Des. 9(2009) 1106-1123.