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# FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLET OF WATER SOLUBLE DRUG BY HOT MELT TECHNIQUE

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## ABSTRACT

Sustained release tablets were prepared by melt granulation method. In present investigation attempt was made to prepare sustain release Matrix Tablet formulation of Timolol hydrochloride using cetostearyl alcohol and hydroxy propyl cellulose. Physical characteristic of prepared blend and evaluation parameters are in limits Batch F5 shows better release profile. So, from that it can conclude that cetostearyl alcohol retard the release of drug in better manner for 24 hrs.

**Key words:** sustain release, timolol, dissolution, melt granulation, wax.

## 1 INTRODUCTION

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets. [1-2].

### 1.1 Advantages

- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.

### 1.2 Disadvantages

- Requires high energy input.
- The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

### 1.3 Techniques for Melt Granulation

*1.3.1 Spray Congealing*

Spray congealing is a melt technique of high versatility. In addition to manufacture multiparticulate delivery system, it can be applied to process the raw meltable materials into particles of defined size and viscosity values for the melt agglomeration process. Processing of meltable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glyceride into an air chamber below the melting point of the meltable materials or at cryogenic temperature. Spray-congealed particles (10– 3000 µm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation[3].

*1.3.2 Tumbling Melt Granulation*

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value. The particle size of a meltable material should be 1/6 or lower than the diameter of the seeds. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity. Both particle size and viscosity of the meltable materials play a significant role in the melting agglomeration process. The control of the melt agglomeration process is best initiated by using meltable materials of controlled properties. For the melt pelletization and melt granulation processes, it is desirable that meltable materials have a high viscosity to improve the mechanical strength of the agglomerates, but a reduced particle size to prevent uncontrollable agglomerate growth. In tumbling melt granulation, small meltable particles with sufficient viscous binding forces are obligatory for the production of spherical beads.Today melt extrusion technology represents an efficient pathway for manufacture of drug delivery systems. Resulting products are mainly found among semi-solid and solid preparations[4].

## 2 MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into four categories.

In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack. Delayed release

- Sustained release
- Site-specific targeting
- Receptor targeting

### 2.1 Sustained Release Drug Delivery Systems

The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule‘s inherent kinetic properties. Thus, optimal design of a sustained/ controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment. Sustained release drug administration means not only prolongation of duration of drug Delivery, similarly to the action in the sustained and prolonged release, but the term also Implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unbeneficial adverse reactions and side effects5.

*2.1.1 Advantages of sustained release drug delivery*

Following are the potential advantages of sustained release products

- Decrease incidence and/or intensity of adverse effects and toxicity.
- Predictable and reproducible release rates for extended duration.
- Maintenance of optimum therapeutic drug concentration in the blood
- Delivery of drug in the vicinity of site of action.
- More efficient utilization of active agent.
- Improved patient compliance.
- Elimination of frequent dosing and wastage of drug, inconvenience of nighttime administration of drug.
- A greater selectivity of pharmacological activity.
- Reduction in GI irritation and other dose- related side effects.

- Enhanced bioavailability.
- Reduction of the incidences and degree of toxic and side effects and irritation of gastro intestinal tract caused by some orally administrated drugs.
- Greater effectiveness in treatment of chronic conditions.
- Enhanced duration of activity for short half-life drugs[6,7].

## 3 CLASSIFICATION OF ORAL SUSTAINED/ CONTRO - LLED RELEASE SYSTEMS

### 3.1 Diffusion Controlled Systems

*3.1.1 Reservoir devices*

A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are

- Zero order drug release is possible.
- The release rate is dependent on the type of polymer.
- High molecular weight compounds are difficult to deliver through the device.

*3.1.2 Matrix devices*

It consists of drug dispersed homogenously in a matrix. The characteristics of matrixdiffusion systems are

- Zero order release cannot be obtained.
- Easy to produce than reservoir devices.
- High molecular weight compounds are delivered through the device.

### 3.2 Dissolution Controlled Systems

*3.2.1 Matrix dissolution controlled systems*

Aqueous dispersions, congealing, spherical agglomeration, etc. can be used.

*3.2.2 Encapsulation dissolution controlled systems*

Particles, seeds, granules can be coated by techniques such as microencapsulation.

*3.2.3 Diffusion and dissolution controlled systems*

In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

## 4 CLASSIFICATION OF MATRIX TABLETS

### 4.1 On the Basis of Retardant Material Used

*4.1.1 Hydrophobic Matrix (Plastic matrix)*

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid[8].

*4.1.2 Lipid Matrix*

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation[9].

*4.1.3 Hydrophilic Matrix*

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one ormore drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups[10]:

- Cellulose derivatives: methylcellulose 400 and 4000 cPs; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.
- Noncellulose natural or semisynthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.
- Polymers of acrylic acid; corbopol , the most used variety.

In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophillic or a hydrophilic polymer matrix.

*4.1.4 Biodegradable Matrix*

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

*4.1.5 Mineral Matrix*

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of seaweeds (Phaephyceae) by the use of dilute alkali[11].

Table-1: Physicochemical parameter for drug selection

| Parameters | Values |
|---|---|
| Mol..ecular weight | <1000 |
| Solubility | >0.1mg/ml |
| Partition coefficient | High |
| Absorption mechanism | Diffusion |
| Absorbability | From all gastrointestional segments |

Table-2: Pharmacokinetic parameters of drug selection

| Parameters | Values |
|---|---|
| Half life | 0.5-8 hrs |
| Total clearance | Not dose dependent |
| Elimination rate constant | Required for design |
| Bioavailability | Should be more than 75% |
| Absorption rate | Greater than release rate |
| Toxic concentration | Safer for dosage form |

## 5 METHODOLOGY

### 5.1 Preformulation Study

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objectives of preformulation studies are to develop a portfolio of information about the drug substance, so as to make information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic-biopharmaceutical properties of the resulting product.

*5.1.1 Solubility of drug*

Solubility of drug was determined in distilled water, ethanol, phosphate buffer (pH 7.4& 6.8), 0.1 N HCl. The solubility of drug is also determined with polymers and wax[12].

Table-3: Solubility profile of Timolol maleate

| Solvent | Solubility ± SD (mg/ml) | Description term |
|---|---|---|
| Distilled water | 3.265±0.154 | Soluble |
| pH 6.8 buffer (PBS) | 1.240±0.149 | Soluble |
| Buffer (PBS pH 7.4 | 7.721±0.353 | Soluble |
| Ethanol | 2.151±0.262 | Soluble |
| 0.1 N HCl | 3.155±0.269 | Soluble |
| Ether | 0.047±0.024 | Practically insoluble |

Table-4: Solubility studies of drug with polymer combinations

| Combination | Average absorbance | Solubility (mg/ml) |
|---|---|---|
| Drug+ HPC | 0.765 | 62.496 |
| Drug + cetostearyl alcohol | 0.679 | 50.393 |
| Drug+HPC +cetostearyl alcohol | 0.667 | 48.393 |

Solubility study of different three combination Drug+ HPC, Drug + cetostearyl alcohol and Drug+ HPC + cetostearyl alcohol was determined spectrophotometrically at 295nm. The minimum solubility of drug is in combination of Drug+ HPC + cetostearyl alcohol. So it will be the final combination for formulation of freely soluble drug.

*5.1.2 Melting point determination*

Melting point of drug was determined by capillary method using melting point apparatus which was found to be 202-206°C

*5.1.3 Partition coefficient*

A measurement of drug's lipophilicity and an indication of its ability to cross cell membranes is the oil/water partition coefficient in systems such as n-octanol/water. The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption, was found 1.34.

### 5.2 Identification of Pure Drug

Identification of pure drug was carried out by FTIR Spectrophotometry (Jasco-4100s, Japan)[13].

*5.2.1 FTIR Spectroscopy*

The FTIR spectrum of pure timolol maleate showed the characteristic peak at 3491 $cm^{-1}$ (O-H stretch of carboxylic acid), 2919 $cm^{-1}$ (C-H stretching of methyl bond), 1734 $cm^{-1}$ (strong C=O stretch of ketone), 1640 $cm^{-1}$ (C=C stretching in the aromatic ring), 1457 $cm^{-1}$ (strong aliphatic C-H bending), 1293 $cm^{-1}$ (aliphatic C-N stretching), 1247 $cm^{-1}$ (C-O stretch), 944 $cm^{-1}$ (N-H wagging) and 850 $cm^{-1}$ (C-H bending). This confirms that the obtained drug is timolol maleate.

### 5.3 Formulation of Preliminary Trial of Timolol Hydrochloride SR Matrix Tablet

Sustained release tablets were prepared by melt granulation method. All the ingredients were passed through sieve 40 #. Weight accurately all ingredients, mixed and heat on water bath with gently stirring. The granules obtained were dried at 60ºC temperature. After drying, granules passed through sieve 20#, 40# and granules retained on 40# to obtained uniform size granules. After sufficient lubrication tablets were prepared using Rimek tablet compression machine. All the prepared blend and timolol hydrochloride tablets were evaluated for different parameters[14].

Sustained release tablets of containing timolol hydrochloride were prepared using cetostearyl alcohol as 30%,35%, and 40% of total tablet weight and hydroxy propyl cellulose as 20%, 25% and 30% of total tablet weight as per given in table.

Table-5: Formulation of batches with timolol hydrochloride, cetostearyl alcohol and HPC (mg)

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Timolol hydrochloride | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| cetostearyl alcohol | 120 | 120 | 120 | 140 | 140 | 140 | 160 | 160 | 160 |
| HPC | 80 | 100 | 120 | 80 | 100 | 120 | 80 | 100 | 120 |
| Dicalcium phosphate | 159 | 139 | 119 | 139 | 119 | 99 | 119 | 99 | 79 |
| Magnesium stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Aerosil | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Total Wt | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

### 5.4 Precompression Evaluation

Before tabletting, the granules were evaluated for moisture content and subjected to micromeritic characterization. Micromeritic properties: The granules were assessed for bulk density, tapped density, compressibility index also, angle of repose was investigated[15,16].

Table-6: Physical characteristics of prepared blend of batches $F_1$ to $F_9$

| Batch | B.D (gm/cc) | T.D (gm/cc) | C.I (%) | A.R (ϕ) |
|---|---|---|---|---|
| **F1** | 0.45 | 0.56 | 19.64 | 30.25 |
| **F2** | 0.44 | 0.57 | 22.80 | 32.54 |
| **F3** | 0.42 | 0.59 | 28.81 | 32.87 |
| **F4** | 0.44 | 0.58 | 25.86 | 30.23 |
| **F5** | 0.45 | 0.59 | 27.72 | 29.37 |
| **F6** | 0.46 | 0.57 | 19.20 | 32.80 |
| **F7** | 0.47 | 0.56 | 16.87 | 33.98 |
| **F8** | 0.43 | 0.54 | 20.37 | 34.65 |
| **F9** | 0.44 | 0.55 | 20.98 | 32.76 |

### 5.5 Evaluation Parameters for Tablets

Prepared tablets were evaluated for certain physical properties like uniformity of weight, thickness, hardness, friability and dissolution study etc[17,18].

Table-7: Evaluation parameters for tablets of batches $F_1$ to $F_9$

| Batch | Thickness (mm) | Hardness $Kg/cm^2$ | Friability (%) | Weight variation(mg) |
|---|---|---|---|---|
| F1 | 4.0±0.2 | 4.8±0.5 | 0.6±0.2 | 402±0.5 |
| F2 | 3.9±0.3 | 5.3±0.3 | 0.6±0.4 | 407±0.2 |
| F3 | 4.0±0.4 | 5.2±0.4 | 0.5±0.1 | 405±0.1 |
| F4 | 4.2±0.1 | 6.1±0.3 | 0.4±0.1 | 401±0.6 |
| F5 | 4.1±0.2 | 5.1±0.2 | 0.5±0.2 | 400±0.4 |
| F6 | 4.6±0.2 | 5.5±0.3 | 0.7±0.2 | 403±0.1 |
| F7 | 4.1±0.4 | 4.6±0.5 | 0.4±0.1 | 408±0.1 |
| F8 | 3.7±0.3 | 5.2±0.4 | 0.8±0.2 | 402±0.2 |
| F9 | 4.9±0.2 | 5.9±0.3 | 0.6±0.1 | 401±0.5 |

### 5.6 Dissolution Studies

Tablets of each formulation were subjected to dissolution studies. In-vitro dissolution studies were carried out to determine the drug release from various formulations. The in vitro drug release study was carried out for 24 hours. The absorbance was determined at λ max of drug. The drug content of each sample was determined from calibration curve.

### 5.7 In Vitro Drug Release Study

The in vitro dissolution study was carried out using dissolution medium consisted of 900ml 0.1 N HCl for first 2hrs followed by phosphate buffer (pH 7.4) from 2 to 24hrs.

Temperature maintained at 37±0.5ºC. Aliquots of 10ml were withdrawn every one hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 295nm spectrophotometricall[19,20]

Table-8: Cumulative % drug release of batches $F_1$ to $F_9$

| Time (hrs) | %Cumulative percentage release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **1** | 18.12 | 17.25 | 15.42 | 14.31 | 15.42 | 12.12 | 9.76 | 6.87 | 5.9 |
| **2** | 28.54 | 26.89 | 22.92 | 19.74 | 21.56 | 18.19 | 12.23 | 10.54 | 12.23 |
| **3** | 36.37 | 33.56 | 27.75 | 23.75 | 29.78 | 24.53 | 29.67 | 18.34 | 17.56 |
| **5** | 45.31 | 42.03 | 32.03 | 30.31 | 35.62 | 33.54 | 37.75 | 30.43 | 28.35 |
| **7** | 56.25 | 54.38 | 42.38 | 41.28 | 58.64 | 59.09 | 51.67 | 47.34 | 45.56 |
| **9** | 69.51 | 67.55 | 56.55 | 53.15 | 68.22 | 66.78 | 73.78 | 49.54 | 47.45 |
| **12** | 81.63 | 79.92 | 68.92 | 64.26 | 75.45 | 74.34 | 76.87 | 59.34 | 62.54 |
| **15** | 93.45 | 88.28 | 76.28 | 70.31 | 86.23 | 82.53 | 83.12 | 67.45 | 65.34 |
| **18** | 99.78 | 99.19 | 98.88 | 84.58 | 90.65 | 83.87 | 82.23 | 83.23 | 78.23 |
| **24** | - | - | - | 94.20 | 98.99 | 92.76 | 89.75 | 87.25 | 83.21 |

The dissolution profile of batches F1 to F9 shows that as the concentration of cetostearyl alcohol increases, the drug release was decrease. This may be due to higher concentration of cetostearyl alcohol which is hydrophobic in nature. It decreases the penetration of dissolution medium in formulations. Batch F5 shows better release profile. So, from that it can conclude that cetostearyl alcohol in 35 % concentration retard the release of drug in better manner for 24 hrs.

## 6 CONCLUSION

Sustained release tablets were prepared by melt granulation method. In present investigation attempt was made to prepare SR Matrix Tablet formulation of Timolol hydrochloride using cetostearyl alcohol and hydroxy propyl cellulose. Physical characteristic of prepared blend and evaluation parameters showed that All batches show good flow properties and compressibility. Hardness of all tablet batches were in range of 5 to 6 and friability was in between 0.4 to 0.6 which was passable.

The dissolution profile of batches F1 to F9 shows that as the concentration of cetostearyl alcohol increases, the drug release was decrease. This may be due to higher concentration of cetostearyl alcohol which is hydrophobic in nature. It decreases the penetration of dissolution medium in formulations. Batch F5 shows better release profile. It was concluded that combination of hydrophobic and hydrophilic polymers better option for sustain release of freely water soluble drugs.

## REFERENCES

1. Chokshi R, Zia H. Hot melt extrusiontechnique: a review, Iranian J Phar Res.2004; 3: 3 -16.
2. Schafer T, Holm P, Kristensen HG. Melt granulation in a laboratoryscale high shear mixer, Drug Devl Ind Pharm. 1990; 16 (8): 1249 – 1277.
3. Heng WS, Wong TW., Melt processes for oral solid dosage forms, PharmTech.2003; 1-6.
4. Evrard B, Delattre L. In vitro evaluation of lipid matrices for the development of a sustained–release sulfamethazine bolus for lambs, Drug Devl Ind Pharm.1996; 22 (2):111-118.
5. Eliasen H, Kristensen HG, Schafer T. Growth mechanism in melt agglomeration with low viscosity binder, Int J Pharm.1999; 186: 149-159.
6. Brabander C. D., Vervaet C., Remon J. P., Development and evaluation of sustained release mini-matrices prepared by hot melt extrusion, J Control Rel. 2003; 89: 235 – 247.
7. Miyagawa Y, Okabe T, Yamaguchi Y. Controlled release of diclofenac sodium from wax matrix granules, J Pharm Sci.1996; 138: 215-224.
8. Sato H,Miyagawa Y, Okabe T. Dissolution mechanism of diclofenac sodium from wax matrix granules, J Pharm Sci.1997; 86: 929-934.
9. Breitenbach J., Melt extrusion: from process to drug delivery technology, Eur J Pharm Biopharm. 2002; 54: 107 – 117.
10. Schafer T, Mathiesen C. Melt pelletization in a high shear mixer. IX. Effect of binder particle size,Int J Pharm.1996; 139: 139-148.
11. Passerini N, Perissutti B, Monoghini M, Voinovich D, Albertini B, Cavallari C, Rodriguez L.Characterization of carbamazepine–

Gelucire 50/13 microparticles prepared by a spray congealing process using ultrasounds, J Pharm Sci. 2002; 91(3): 699-707.

12. Maejima T, Osawa T, Nakjima K, Kobayashi M. Application of tumbling melt granulation method for preparing controlled release beads coated with hydrogenated castor oil, Chem Pharm Bull.1997; 45(5): 904-910.

13. Kidokoro M, Sasaki K, Haramiishi Y, Matahira N. Effect of crystallization behavior of polyethylene glycol 6000 on the properties of granule prepared by fluidized hot melt granulation (FHMG), Chem Pharm Bull. 2003; 51 (5): 487–493.

14. Kaufman HS, Falcetta JJ. Introduction to polymer science and technology: an SPE textbook, 1st ed. New Yolk: John Wiley & Son 1977;.

15. McGinity JW, Zhang F, Repka MA, Koleng JJ. Hot-melt extrusion as apharmaceutical process. Am Pharm Rev. 2001; 4(2): 25-36.

16. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002; 54:107-117.

17. Crowley MM, Zhang F, Koleng JJ, McGinity JW. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion, Biomaterials. 2002; 23:4241-4248.

18. McGinity J, Hot-melt extrusion as a pharmaceutical process. AAPS Newsmagazine. 2004; 7(3):21–25.

19. Dittgen M, Fricke S, Gerecke H, Osterwald H. Hot spin mixing: a new technology to manufacture solid dispersions, Pharmazie.1995; 50:225–226.

20. Patel PS, Mundargi RC, Ramesh Babu V, Jain D, Rangaswamy V, Aminabhavi TM. Microencapsulation of doxycyline into Poly(lactideco-glycolide) by spray drying technique: Effect of polymer molecular weight on process parameters. J App Poly Sci. 2008; 108:4038-4046.