Use of Microwave in Processing of Drug Delivery Systems

T.W. Wong*

Particle Design Research Group, Faculty of Pharmacy, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia

Abstract: Microwave has received a widespread application in pharmaceuticals and food processing, microbial sterilization, biomedical therapy, scientific and biomedical analysis, as well as, drug synthesis. This paper reviews the basis of application of microwave to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, tablets and film coat. The microwave could induce drying, polymeric crosslinkages as well as drug-polymer interaction, and modify the structure of drug crystals via its effects of heating and/or electromagnetic field on the dosage forms. The use of microwave opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process or toxic reactants. Alternatively, the microwave can be utilized to process excipients prior to their use in the formulation of drug delivery systems. The intended release characteristics of drugs in dosage forms can be met through modifying the physicochemical properties of excipients using the microwave.

Keywords: Agglomerates, excipient, film coat, gel beads, microspheres, microwave, solid dispersion, tablet.

INTRODUCTION

Microwave is an electromagnetic wave which has frequencies between 300 MHz and 300 GHz, equivalent to wavelengths of 1 m to 0.01 m [1-2]. Microwave is generated by a magnetron, a device which converts the electrical energy into an alternating electromagnetic field [3]. The magnetron consists of four components: an anode block, a cathode filament, a pair of permanent magnets and an antenna. The production of microwave begins when an electron is emitted by the cathode filament and accelerated towards the anode block, making spiral movements under the influences of applied electric and magnetic fields. The electromagnetic field alternates its charge at a high frequency. This current is carried by an antenna and released as microwave through the waveguide.

The interaction propensity between the microwave and processing material can be described by doses of energy transferred to the object using the following equation [4]:

\[ D_{abs} = W_{abs} \times t \]  

where \( D_{abs} \) = dose of microwave radiation absorbed, \( t \) = time, and \( W_{abs} \) = power of microwave radiation absorbed of which is denoted as difference between the nominal power, \( W \), and the reflected power, \( W_{ref} \).

\[ W_{abs} = W - W_{ref} \]  

It is mainly governed by the physicochemical attributes of material, microwave and processor, namely microwave frequency and power [1, 5-8], material mass [1, 5], density [5], shape [5, 10-11], moisture content [1, 5, 12-13], temperature [1, 5-7], electrical conductivity [5, 14], thermal conductivity [5] and specific heat [5], as well as, processor geometry [10, 15].

Principally, the microwave is not a form of heat, but a form of energy which manifests as heat through its interaction with materials via ionic and particularly polar excitation of the object molecules. The permittivity, \( \varepsilon \), of materials sensitive to microwave is constituted of real part, \( \varepsilon' \), or relative dielectric constant, as well as, imaginary part, \( \varepsilon'' \), or loss factor. The dielectric loss factor, \( \varepsilon'' \), is a measure of propensity of heat generated inside a material per unit time when the microwave is applied. The rate of temperature rise in a material which absorbs the microwave energy can be represented by [14]:

\[ \Delta T / \Delta t = P_e / \rho C_p \]  

and

\[ P_e = j \varepsilon' \varepsilon'' \varepsilon'' + j \varepsilon' \varepsilon'' \tan \delta \]  

where \( \Delta T \) = temperature rise (K), \( \Delta t \) = time (s), \( P_e \) = power per unit volume of material (W/m³), \( \rho \) = density (kg/m³), \( C_p \) = heat capacity (J/kg.K), \( E \) = electrical field strength (V/m), \( f \) = frequency (Hz), \( j \) = constant, \( \varepsilon'' \) = dielectric loss factor, \( \varepsilon = \) loss tangent or dissipation factor, and \( \varepsilon' \) = relative dielectric constant or relative permittivity.

The dielectric characteristics of a material are governed by a number of factors, such as, material composition [2, 6, 11, 14, 16], moisture content [5, 11, 14, 17], density [2, 5, 14] and temperature [2, 5-6, 11, 14, 17-18]. The dielectric constant of a material is related to the polarizability of its constituents and the loss tangent is regarded as a measure of molecular interaction [19]. Polar materials with a high level of molecular interaction are expected to absorb more energy, giving rise to a more intense molecular vibration and heat.

APPLICATIONS OF MICROWAVE IN PROCESSING OF DRUG DELIVERY SYSTEMS

There is a widespread use of microwave in food [20-22], microbiological [20-21, 23-26], biomedical [27-30], analytical [31-33] and drug discovery [34-36] applications. In the recent decade, the microwave has been utilized to process dosage forms such as polymeric gel beads [19, 37-39], microspheres [40], nanomatrix [41], agglomerates [4, 42-48], tablet [13, 50], film coat [51] and solid dispersion [52]. The drug delivery systems are processed and modified via the heating and/or electromagnetic elements of microwave. The microwave can be introduced during the preparation process of dosage forms and/or directly onto the pre-formed products (Fig. 1). Alternatively, the microwave can be applied to process the excipients prior to their use in the formulation of drug delivery systems (Fig. 1) [50, 53-63]. In the latter, the physicochemical properties of excipients can be specifically modified by microwave to provide the intended release properties of drugs in dosage forms.

Agglomerates

The drying of wet mass involves two concurrent processes: transfer of internal liquid to the mass surfaces and transfer of energy from the surrounding environment to evaporate the surface liquid [14]. The rate of wet mass drying is governed by the propensity of surface liquid evaporation and internal liquid migration from the core to the exterior of drying mass. Practically, the rate of liquid removal from the surfaces of the wet mass is dependent on the temperature [14, 49, 64], relative humidity [14, 49, 64], air flow [10, 14, 65], pressure [14] and exposed surface area [14] of the surrounding environment. On the other hand, the rate of liquid migration from the core to surfaces of wet mass is affected by the liquid content [14, 64], temperature [14, 49], physical [14] and thermal [14, 49, 66] properties of the material. In the pharmaceutical indus-
The introduction of microwave offers a faster alternative mode of drying. The microwave has been applied in drying of granules produced by fluid-bed granulator, low speed mixer and high shear granulator in the same process of agglomeration [4, 43, 45-46, 48]. The rate of liquid removal by microwave can be modified through the use of vacuum and/or hot air in the same drying process [16, 43, 45-46, 48]. The drying mechanism of microwave involves the transfer of microwave energy to agglomerates, vibration and evaporation of solvent molecules of the binding liquid by heat. The microwave could induce reversible electron, ion, orientational and deforming dielectric polarization, and result in heat being generated from both the solvent and agglomerate constituents [4]. In accordance to Debye’s theory, this heat is liberated as a result of the very intensive friction of molecules in the high frequency field force [4]. The heat, to a lesser extent, may be obtained from the emission of absorbed surplus energy by electrons which have formerly activated to higher energy levels, following dynamic reorganization. Typically, the loss factor of agglomerate constituents is lower than that of solvents (Table 1). The microwave energy is preferentially absorbed by the solvent molecules. The solvent molecules have a greater inclination to be heated under the inductive effect of microwave. This in turn gives rise to quick drying of agglomerates at reduced energy expenditure.

Table 1. Loss Factors of Some Examples of Pharmaceutical Materials and Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Loss Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>8.60</td>
<td>[42, 16]</td>
</tr>
<tr>
<td>Iso-propanol</td>
<td>2.90</td>
<td>[42]</td>
</tr>
<tr>
<td>Acetone</td>
<td>1.25</td>
<td>[42, 16]</td>
</tr>
<tr>
<td>Pure water</td>
<td>6.10</td>
<td>[42, 16]</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.02</td>
<td>[42, 45]</td>
</tr>
<tr>
<td>Maize starch</td>
<td>0.41</td>
<td>[42, 45]</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>0.15</td>
<td>[45, 123]</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.06</td>
<td>[45, 123]</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>0.06</td>
<td>[45, 123]</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>0.03</td>
<td>[45, 123]</td>
</tr>
</tbody>
</table>

The rate of drying the agglomerates by means of microwave is largely governed by the loss factor of granulation excipients and granulating liquids [42-43, 45], material load [67-68], microwave frequency and power [4, 43], air flow temperature and velocity [16], as well as dryer design and mixer motion [43, 67]. In one study by McLoughlin et al. [16], it is found that the drying kinetics of pharmaceutical materials is affected by the latent enthalpy and boiling point of the solvents to a greater extent than that of loss factor. The use of high loss excipients as the granulation materials may delay the process of drying as such excipients could absorb microwave readily when compare to that of solvent [42]. Principally, an appropriately designed microwave dryer should have a good capacity to localize the microwave energy onto the processing mass by containing the energy and restricting the flow of free or reflected microwave from the dryer [43]. With respect to the efficiency of microwave usage, it has been reported that the laboratory equipment is less efficient than the large scale processor owing to its small ratio of chamber capacity to product volume [43]. The dielectric and thermal properties of a complex pharmaceutical composition are rarely known [67]. In fact, these properties vary during the course of drying, thus making an accurate control of the drying process by means of material characteristics less feasible.

Practically, the agglomerates have been found to undergo reversible heteromorphic solid state alteration following the irradiation of microwave [4]. The microwave could induce changes of temperature, physical phase, size, specific surface area, solid state structure and electrodynamic nature of agglomerates, as well as, covalent, ionic, ionic, interaction, van der Waals and metallic bonds alterations of the materials [4]. The agglomerates produced from the high shear granulator and dried using the microwave have a lower level of porosity, higher levels of roundness, bulk and tapped densities than those of dried using the fluid-bed hot air technique [48]. These agglomerates require higher compression forces in the production of compact, but the mass distribution and disintegration time of the formed tablets are unaffected by the choice of drying method [48]. Under the influence of microwave, the propensity of drug migration from the core to the exterior of agglomerates becomes remarkably lower than that of dried using the hot air oven as drying by microwave involves heating and vaporization of liquid throughout the bed of granulating mass thereby eliminating the gradient of granulating liquid needed for drug migration [47]. In another studies by
Mandal [44], and Doelling and Nash [43], the introduction of microwave in drying of wet agglomerates has nevertheless reported to have no influence on the size, morphology, drug dissolution, hardness, compressibility, loose and tapped bulk densities, as well as, tablet compression characteristics of agglomerates. The agglomerate is made of several chemical constituents. The extent of changes brought about by microwave is dependent on the overall electrodynamic physical properties of agglomerates. In a closed-loop agglomerator, the maximum and minimum field forces of microwave display sinusoidal changes in the irradiated space between stationary waves. The influences of microwave could vary with agglomerate volume, geometry of agglomerator, agglomerate massing intensity, microwave frequency and power, thereby leading to dissimilar changes in the physicochemical properties of dried products.

Gel Beads/Microspheres

Gel Beads

Polymers, such as pectin and alginate, have been widely employed as the matrix carrier for small molecule drugs [65-91]. The widespread application of these polymers to microwave is attributed to their biodegradability and low oral toxicity. Nonetheless, the embedded drug molecules exhibit a fast rate of drug release via diffusion through the pores of the matrix. Such rate of drug release is undesirable in the case of the need to target the drugs to the lower part of gastrointestinal tract, particularly, the colon.

Over the past 10 years, various formulation and processing approaches have been taken to negate the rate of drug release from these polymeric matrices, but with varying degree of success. High concentrations of multivalent metallic cations such as Ca$^{2+}$ and Zn$^{2+}$ or non-metallic cations such as poly-L-lysine have been employed as crosslinking agents for pectinate and alginic matrices [69, 74, 76, 78, 81, 85-86, 90-91]. The effects of drug/polymer ratio, molecular weight and chain conformation of pectin and alginate on the drug release property of polymeric matrices have been examined [69, 71, 82, 87]. The pectin and alginate have been subjected to coacervation with chitosan to form the polyelectrolyte complex of which is envisaged to have a higher drug release retardation capacity than that of the individual substance [80, 87]. Attempts to coat or incorporate the polymeric matrix with hydroxypropylcellulose and other excipients have been initiated in view that such materials could serve to retard the release of small molecule drugs such as theophylline, sulphasalazine and diclofenac sodium [72, 75, 78, 81, 84, 88-89]. Aldehyde, a reactive chemical agent, has also been used to crosslink the polymeric matrix in order to alleviate the propensity of drug loss from the matrix [73].

Lately, the microwave has been utilized to modify the state of molecular interaction between the chains of alginate and pectin, with the aim to further delay the release of small molecule drugs such as diclofenac sodium and sulphathiazole from the gel beads prepared from these polymers [19, 37-38]. In addition, gel beads prepared from the coacervation of alginate and pectin with chitosan or chitosans alone, as well as, gelatin microspheres have been subjected to the treatment of microwave for the same purpose [19, 37-38, 40]. The alginate, pectinate, alginate-chitosonium, pectinate-chitosonium and chitosonium gel beads are prepared by means of extrusion method and crosslinked using bi- or multi-valent countergions. The gelatin microspheres are formed using the emulsification-extrusion method and crosslinked using bi- or multivalent countercations. The extent and rate of drug released from the microwave-treated gel beads is greatly increased in spite of drug-pectin interaction is effected via the C=O moiety of COOH and/or COOCH$_3$ of the polymer [38]. The extent and rate of drug released from the microwave-treated gel beads is greatly increased in spite of drug-pectin interaction is effected via the C=O moiety of COOH and/or COOCH$_3$ of the polymer. The extent and rate of drug released could not be merely reduced through the coacervation of pectinate matrix with chitosan, but requiring the introduction of both microwave and chitosan to effect further coacervation and drug release retardation (Fig. 2).

Essentially, the treatment of gel beads at varying intensities of microwave irradiation may not bring about similar drug release profiles, though the level of microwave energy supplied is kept identical. This is inferred from the latest study of gel beads prepared from poly (methyl vinyl ether-co-maleic acid) polymer [39]. Apparently, the propensity of drug released from the poly (methyl vinyl ether-co-maleic acid) gel beads is markedly enhanced through treating the samples by microwave at 80 W as a result of loss of polymer-polymer interaction via the COOH moieties, but decreased upon treating the same batch of beads by microwave at 300 W following polymer-polymer interaction via the O-H, COOH and COO$^-$. As well as, drug-polymer interaction via the N-H, O-H, COO$^-$ and C-O moieties. Using Korsmeyer-Peppas equation, it is found that the mechanism of drug release tends to follow the zero order kinetics. The drug release is markedly governed by the state of polymer relaxation of the matrix of which in turn could be affected by the state of polymer-polymer and drug-polymer interactions in the beads. Under the influence of microwave, the aged gel beads give rise to different drug release profiles than those of freshly prepared samples [19]. The aged alginate gel beads require intermittent cycles or longer duration of microwave irradiation to retard the release of drug from the matrix in contrast to their freshly prepared counterparts. Unlike the alginate gel beads, the drug release retardation property of aged alginate-chitosonium gel beads can be significantly enhanced through subjected these beads to a single cycle or a shorter duration of microwave irradiation. There is no further change in drug release profile from these gel beads beyond one cycle of microwave irradiation. With reference to the influences of microwave, the drug release property of polymeric gel beads, of both water-soluble and water-insoluble drugs such as sodium diclofenac and sulphasalazine respectively, is mainly governed by the state of polymer-polymer and/or drug-polymer interaction of the matrix [19, 37-38]. There is no clear relationship between the profile of drug release and type of predominant polymorphs in the polymeric matrix. In alginate and alginate-chitosonium gel beads treated by microwave, the changes in crystallite characteristics of drug are indeed hindered by drug-polymer interaction [19, 37]. The reduction in the extent and rate of drug released from these gel beads is primarily brought about by the formation of non-ionic bonds and/or polymer coacervation. Unlike alginate gel beads, the level of polymer-polymer interaction is higher in aged alginate-chitosonium beads than the corresponding fresh samples. The aged alginate-chitosonium gel beads thereby require a shorter duration of microwave irradiation to retard the drug release than that of the freshly prepared matrix. In the case of pectinate gel beads, the extent and rate of drug released from the matrix is enhanced by the microwave following a reduction in the propensity of pectin-pectin interaction via the C=O of COOH and/or COOCH$_3$ of the polymer [38]. The extent and rate of drug released from the microwave-treated gel beads is greatly increased in spite of drug-pectin interaction is effected via the C=O moiety of COOH and/or COOCH$_3$ of the polymer. The extent and rate of drug released could not be merely reduced through the coacervation of pectinate matrix with chitosan, but requiring the introduction of both microwave and chitosan to effect further coacervation and drug release retardation (Fig. 2).
Over the past 40 years, numerous difficulties are encountered in design of solid dispersion, thereby limiting its commercial application in the pharmaceutical industry. Preparation of solid dispersion by the melting method involves heat, which may lead to decomposition or evaporation of the drug particles and/or matrix former [94-95, 115]. On the other hand, the solvent method demands a high operating cost for solvent, flame-proof facilities, solvent removal and recovery systems [94-95]. The drug particles in the solid dispersion prepared by either method have poor physicochemical stabilities and their dissolution properties are affected appreciably by the storage conditions such as length of time [94-95, 101-102, 114-115, 117], temperature [94-95, 102, 115] and humidity [95, 104, 114-115]. The dissolution of solid crystalline drugs is promoted by forcing the drug crystals to assume a microstructure characterized by nanoscale periodicity and/or disordered metastable phase [41]. Nonetheless, it is technically difficult to “freeze” the metastable drug phases in a physically and chemically stable drug delivery system.

Alternatively, the dissolution of poorly water-soluble drugs may be enhanced through the conversion of drug particles into interactive mixture using a soluble carrier system [96-99, 110]. In this system, fine drug particles are distributed onto coarse carrier particles. The aggregation level of drug particles is reduced, thereby increasing their propensity of dissolution [96, 99]. The preparation of interactive mixture avoids the use of heat and solvent, and it is an economical one-step process. The physicochemical stabilities of drug and carrier particles are affected to a smaller extent by the preparation process than those of prepared by the melting and/or solvent methods. Nonetheless, the degree of drug dissolution enhancement is less satisfactory with the use of interactive mixture than that of solid dispersion.

Recently, Keré et al. [52] and Bergese et al. [41] have explored the usefulness of microwave as the alternative mode of preparation for solid dispersion. In the former, the physical mixture of both felodipine drug and porous amorphous silicon dioxide carrier is subjected to microwave treatment at 500 W for different periods of time, between 5 and 15 min. The drug release propensity is higher in samples subjected to microwave irradiation for a longer period of time. The drug release propensity of microwave-treated physical mixture is greatly higher than those of pure drug, physical mixtures which are untreated by microwave or treated by vacuum at 100°C, or obtained using solvent deposition method. These observations are ascribed to a reduction in the level of crystallinity of drug following its treatment by microwave in the form of a physical mixture. The use of crystalline sodium chloride as carrier brings about similar changes to the amorphousness of drug in physical mixture treated by microwave, whereas a minor modification of drug crystallinity is noted when solvent deposition or vacuum method is employed to prepare the solid dispersion of felodipine and sodium chloride.

The microwave has also been utilized to produce solid dispersion using the concept of hybrid heating [41]. Low loss pharmaceutical materials have a poor electrothermal coupling capacity with microwave. They are difficult to be heated by microwave at room temperature. Nevertheless, they could absorb the microwave energy upon preheating to a suitable temperature and beyond which they will couple with the microwave. Using a high loss reactor, the reactor could absorb the microwave energy readily at a low temperature, convert the energy to heat, and transfer the heat to the low loss pharmaceutical materials by diffusion which in turn promotes the coupling capacity of processing mass with microwave. The solid dispersion prepared thusfar via hybrid heating includes nanomatrix with nanocrystals and molecular clusters of drug embedded in the core, and microcrystals of drug adhered onto the surfaces of matrix [41]. Practically, the processing of nanomatrixes of water-insoluble drugs such as ibuprofen, nimesulide and nifedipine embedded in matrix substances such as crospovidone and β-cyclodextrin by mi-
microwave could result in drug transforming from microcrystals to molecular clusters and lowering in the crystallinity level of nanomatrices to less than 30% [41]. This in turn is envisaged to enhance the dissolution propensity of water-insoluble drugs.

**Tablet/Film Coat**

**Tablet**

The use of microwave has a strong implication in design of sustained-release drug delivery systems such as matrix and coated tablets. Frequently, the sustained-release property of a tablet is imparted by the judicious choice of polymeric retardants. Ispaghula husk, the dried seed coats of *Plantago ovata*, has been employed in the manufacture of matrix tablets [50]. The fibers of Ispaghula husk are not readily absorbed or digested by the body. The husk forms gel upon in contact with water but the formed gel structure is weak and disrupts upon manual agitation. The poor gel formation tendency of Ispaghula husk may be attributed to its incomplete swelling and this negates the sustained-release characteristics of the husk (Fig. 3) [50]. Incidentally, the tablets prepared from the husk are found to be soft. The modification of Ispaghula husk by hot air treatment does not appear to be able to induce rigid gel formation. The hot air treatment does not yield husk which is suitable for use in manufacture of sustained-release tablet. Prolonged heating of Ispaghula husk may bring about polymer degradation and thus the network of polysaccharide needed to sustain the release of drug is lost (Fig. 3) [50].

Treatment of Ispaghula husk by microwave has shown to introduce superior swelling and rigid gel formation properties to the husk (Fig. 3), in both distilled water and simulated gastric fluid (pH 1.2) [50]. The matrix tablets prepared from microwave-treated Ispaghula husk swell considerably and do not erode during the in vitro dissolution testing. The drug release profile of such tablets is not significantly altered by the pH of the dissolution medium as well as the rate of paddle rotation. The sustained-release property of Ispaghula husk tablet is brought about by the hydration of husk particles and network formation between long chain polysaccharide molecules. The release of drug from Ispaghula husk tablet is effected via diffusion through the pores of the swollen matrix.

In another research study by Qasem [13], the microwave is found to be able to reduce the rate and extent of drug released from the matrix tablet made of water-soluble bovine serum albumin protein. On the contrary, it is not able to retard but instead induce a significant rise in the rate and extent of drug released from matrix tablet made of water-insoluble gluten protein. During the process of tablet preparation, the bovine serum albumin matrix can be easily sorbed with moisture and thermally denatured by means of microwave. The matrix tablet could produce polymeric crosslinkages readily upon irradiated by microwave thereby able to retard the drug release. The extent of drug release retardation is higher with an increase in the content of sorbed moisture and time length of microwave irradiation. The gluten matrix tablet, on the other hand, has a poor capacity to sorb moisture. The thermal denaturation activity of microwave is mainly restricted to the hydrophilic core fraction of gluten but not the hydrophobic fraction of gluten at the external surfaces of matrix tablet. The latter fraction of gluten protein fails to aggregate thereby leading to an increase in hardness but no marked retardation of drug release of the matrix tablet.

**Film Coat**

The drug release property of a tablet is modifiable by the addition of a polymeric coat onto the matrix. The polymer coat is commonly introduced to the tablet from an aqueous solution or suspension of polymer. The drying of polymeric coat can be effected by microwave and/or hot air. It has been found that the application of microwave to dry the polymeric coats, such as films of hydroxypropylmethylcellulose or methycellulose, does not markedly alter their water vapor permeability [51]. One reason is that the microwave does not result in bubbling of coating solution or gross film coat defects which compromise the coat integrity under optimal irradiation conditions [51]. The film coat dried using microwave is more elastic, but possesses a slightly lower level of tensile strength than that of dried using the hot air current. Ideally, a film coat should be both strong and elastic with respect to its function as controlled-release barrier of drugs. The ratio of tensile strength to Young’s modulus of microwave-dried film coat has been found comparable or larger than that of oven- or air-dried films [51]. In addition, drying of polymeric film coat by microwave is 16 to 22 times faster than that of by hot air current [51].

**Excipient Processing**

Polymers are commonly used in design of controlled-release drug delivery systems. Processing of polymers by microwave can lead to changes in their physicochemical properties such as adsorption, capacity, absorbency, molecular weight, aqueous and/or organic solubility through drying, polymerization or depolymerization process [50, 53-63]. The use of microwave processed polymers is therefore envisaged to give rise to drug delivery systems of different physicochemical attributes and drug release profiles.

The depolymerization effect of microwave has been exploited in synthesis of shorter oligogluconsamine chains by oxidative degradation of chitosan, a larger molecular weight parent polymer, with neutral hydrogen peroxide [54]. The oligogluconsamine is formed with amino functional group of chitosan remained undestroyed by the process of oxidative degradation. The yield of oligogluconsamine is strongly dependent on reaction time and concentration of hydrogen peroxide. Alternatively, the hydrolysis of chitosan to oligomers can be effected by microwave using the sodium chloride [57].

The polymerization effect of microwave is used in synthesis of copolymers or larger molecular weight substances. Examples of such products are copolymers of lactic acid and/or glycolic acid [13], maleic anhydride and allylthiourea [13], chitosan and acrylic acid [60], chitosan and polyacrylamide [61], chitosan and poly(methylmethacrylate) [62], as well as, carboxymethyl chitosan [63], phthaloylchitosan [59] and sulfated chitosan [58].

**GENERAL REMARKS**

There is a wider spread application of microwave in processing of agglomerates than of other dosage forms. In the case of the former, the microwave is utilized mainly as the source of heating and drying of the drug delivery systems during their course of production. Till now, there is limited number of studies which focus on the effects of microwave on the physicochemical properties of excipients and drugs, as well as, the drug release properties of the formed products. The information which describes the effects of loss factor, thermal conductivity, electrical conductivity, specific heat, moisture content, porosity, size, shape, temperature and other physicochemical attributes of pharmaceutical formulations on drug release in relation to the influences of microwave is lacking.

Previous studies indicated that the use of microwave in pharmaceutical processing is borne with various risks. Frequently, the distribution of electromagnetic field and thus the temperature across the processing materials is rather heterogeneous [67-68]. It is envisaged to lead to a high level of non-uniformity in the modifications imparted to the dosage forms and could result in irreproducible drug release pattern. The use of microwave could propagate the formation of hotspot [67-68]. There is a high risk of product degradation by localized heat when the thermal diffusivity of the processing materials is low in which the heat flow is slower than the rate of energy dissipation [67-68]. Expectedly, the microwave is not appropriate for use to process liquid dosage form as the aqueous medium could accentuate the intensity of physical and chemical deg-
radation of drugs and excipients by microwave through its high loss and heating characteristics. The use of microwave under a vacuum environment during the process of drying carries hazards of fire explosion [42]. The leakage of microwave into the surrounding ambience can bring about biological tissue heating [42]. The human body absorbs electromagnetic radiation of frequency higher than 15 MHz [120]. The intensity of microwave absorption varies with the parts of human body. Low intensity of microwave has been found to induce biochemical and physiological changes of rats [121-122]. In association with the application of microwave in drug delivery system processing, it is therefore imperative to conduct pharmaceutical research for the need to further understand the mechanism of action of microwave in modifying the drug release properties of dosage forms, as well as, to justify the advantages of microwave for use in processing of drug delivery systems.

CONCLUSIONS

There is a widespread application of microwave in food processing, microbial sterilization, biomedical therapy, scientific and biomedical analysis, as well as, drug synthesis. In recent years, the microwave is utilized to process drug delivery systems such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, tablets and film coat. Practically, the microwave could induce drying, polymeric crosslinkages and drug-polymer interaction, as well as, modify the structure of drug crystallites in dosage forms via its effects of heating and/or electromagnetic field. The microwave can be applied during the preparation process of dosage forms and/or onto the pre-formed products. Alternatively, it can be employed to process the excipients prior to their use in the formulation of drug delivery systems. The use of microwave opens a new route to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms. It provides the intended release characteristics of drugs in dosage forms without the need for excessive heat, lengthy process and/or toxic reactants. The net outcome of drug released from a dosage form is dependent on the interplay between microwave, drugs and excipients.

REFERENCES


Received: March 15, 2007 Revised: December 17, 2007 Accepted: January 09, 2008