Chapter 2

Review of Literature
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2.1 Disintegration, Dissolution and Bio-availability from hard capsules.

2.1.1 Storage conditions and cross-linking

Meyer et al.\textsuperscript{1}, reported that highly stressed acetaminophen capsules were not bioequivalent compared to non-stressed hard gelatin capsules. They failed in dissolution criteria even in presence of simulated gastric fluid USP.

Digenis et al.\textsuperscript{2}, studied rupture behavior of capsules in vivo. They also carried out a six-way single dose bioequivalence study for stressed amoxicillin capsules. The study showed a delay in the in vivo capsule rupture of severely cross-linked capsules, which then led to a delay in the onset of absorption and $T_{\text{max}}$.

Manikandan and Singh\textsuperscript{3} conducted studies on dissolution of ibuprofen hard gelatin capsules stored at high temperature and high humidity, with and without light. The drug release was retarded when light was included with the two other accelerated conditions.

Digenis et al.\textsuperscript{4}, reviewed the causative factors and mechanism of cross-linking of gelatin. The effect of formulation, packaging, high humidity, high temperature and exposure to light have been reported.

Dey et al.\textsuperscript{5}, showed that etodolac capsules (200 or 300 mg), when stored at accelerated conditions (40°C and 75% RH) unpacked or packed in poly(vinyl chloride) (PVC) or PVC– polychloro-trifluoro-ethylene blisters, failed to meet the dissolution specification of 80% Q in 30 min, but the capsules those were stored in high-density
polyethylene (HDPE) bottles continued to confirm to the dissolution specifications.

Kontny et al.\textsuperscript{6-7}, reported that transfer of moisture from shell to fill and vice versa may result in stability problems, retardation of disintegration in the products containing gelatin.

Murthy et al.\textsuperscript{8-9}, studied the effect of exaggerated storage conditions on the dissolution characteristics of hard-shell capsule preparations using three drugs. Mohamad\textsuperscript{10} observed partial insolubilization of gelatin shell for tetracycline HCl capsules stored for 48 months. Ludwig et al.\textsuperscript{11-12}, reported that hard gelatin capsule ruptures first at shoulders of the cap and body where the shell is the thinnest.

Bremecker and List\textsuperscript{13} studied the influence of relative humidity on drug release from hard gelatin capsules in vitro. Chlordiazepoxide, nortriptyline HCl, pericyazine and procaine HCl were filled in capsules. The drug dissolution study was carried out in flow through cell. The effect of moisture content of shells along with relative humidity of storage condition retarded dissolution of API under excessive moisture content.

York\textsuperscript{14} prepared sorption-desorption isotherms for studying the effect of powder moisture content on drug release from barbitone containing hard gelatin capsules.

Ludwig et al.\textsuperscript{15}, studied the disintegration of hard gelatin capsules analysis of type of gelatin, iso-electric point, film properties of gelatin, structure of hard capsules were carried out. The wall thickness and wall structure was found out. The study conducted that Type B gelatin was better for disintegration.
Juhl and Blaug\textsuperscript{16} studied the factors affecting release of medicaments from hard gelatin capsules. Chloramphenicol and tetracycline capsules were subjected to disintegration testing. The effect of temperature and pH of the dissolution medium (1-9) was studied. They found that 37°C and acidic pH was more favorable to dissolution.

Schmitt and Mathis\textsuperscript{17} discussed the problems arising in the industrial production of hard gelatin capsules with attention to disintegration, drug availability, physical properties of the contents, storage and product stability in presence of light, moisture and oxygen.

Langenbucher\textsuperscript{18} observed retardation of dissolution in capsule formulation containing lactose after 2-8 weeks of storage at 11-67% RH. Prista et al.\textsuperscript{19}, studied the effect of UV light and heat on menadione hard gelatin capsules. Chemical stability against UV light was compared in shells of different colors. The effect of storage conditions like heat and UV light were studied by USP disintegration test.

Delonca et al.\textsuperscript{20}, studied the influence of excipients and conditions of storage on capsules containing aspirin. Dicalcium phosphate, calcium sulphate, maize starch were used as diluents. Polyvinylpyrrolidone, sodium alginate and talc were used as excipients. The effect of storage conditions like temperature, relative humidity and light were studied.

Ito et al.\textsuperscript{21}, studied water vapor transfer between capsules and excipients. The shells used were colorless as well as opaque. Diluents such as lactose, maize starch and potato starch were used in the
study. Colorless shells exhibited more deteriorating effect in presence of high humidity. Stability testing was also carried out.

Gore and Ashwin\textsuperscript{22} studied the effect of relative humidity on hard gelatin capsules containing semi-synthetic penicillins. Leupin\textsuperscript{23} developed stability testing experiments for hard gelatin capsules. Strickland and Moss\textsuperscript{24} studied the effect of moisture content on shells and contents, moisture transmission study and effect of stearic acid coating on hard gelatin capsules.

2.1.2 Choice of excipients and processing

\textit{General excipients}

Kuntz and Rothlirberger\textsuperscript{25} found optimal amount of water in liquid fill masses for hard gelatin capsules by means of textual analysis and experimental design. Hydrophillic polymer mixture and amphiphilic mass with high HLB value was filled in hard gelatin capsules. PVP K-17 exhibited little influence on balance amount of water in the range of 10-12\% w/w. Labrasol kept initial stiffness with 5-6\% w/w. The study revealed that long term study is needed for final statement between formulation and hard gelatin capsules.

Pifferi et al.\textsuperscript{26}, presented a review on excipient harmonization and standardized functionality test. The authors opined that expert systems will contribute to change the conventional trial and error formulations approach into a far more scientific and technological development.

Combes et al.\textsuperscript{27}, studied the influence of diluents on the rate of release of two non-steroidal anti-inflammatory drugs from capsules.
Aspirin and indomethacin were subjected to continuous flow type dissolution testing. The results were subjected to factorial analysis.

Kassem et al., reported the effect of certain additives on the dissolution rate of chloramphenicol. Solid dispersions were prepared by fusion method. Use of surfactants from natural source like dehydrocholic acid, sodium deoxycholate, synthetic surfactants like macrogol esters, macrogol ethers and sodium lauryl sulphate were used. Adsorbent like colloidal silica was used to prepare dry solid dispersions. Various grades of adsorbents were also used and diluents like dextrose, lactose, sucrose were used. The formulations were subjected to dissolution testing after filling them in hard gelatin capsules.

Jones reviewed the influence of excipients on design and manufacturing of tablets and capsules. Fundamental and derived properties of excipients influence the caking, packing, flow characteristics and compact formation. The selection of each excipient can be based upon its relevant physical characteristics. The knowledge of moisture of sorption and compaction properties is essential.

Nerlo studied the effects of excipients on properties of oral solid dosage forms including hard capsule formulation and compared the results with tablets and soft gelatin capsules.

Newton and Razzo reported the influence of additives on the in vitro release of drugs from hard gelatin capsules. Nitrofurantoin, nitrofurazone, oxytetracycline dihydrate, tetracycline HCl were used as model drugs. Lactose, sodium starch glycolate, dry flow starch, magnesium stearate and lactose were used as excipients. The
capsules were subjected to beaker dissolution testing method and effect of formulation was studied.

_Diluents and Adsorbents_

Felton et al.\textsuperscript{32}, studied the effect of microcrystalline cellulose, silicified microcrystalline cellulose (SMCC), high density SMCC and microcrystalline cellulose with fumed silica. Both silicified derivatives exhibited better flow than plain. A relationship was established between compressibility and weight variation. On the other hand no relationship was observed between powder flow and weight variation.

Patel and Podczeck\textsuperscript{33} investigated the effect of type and source of microcrystalline cellulose capsule. Medium and coarse grade granules were found to be better than fine grade.

Ari-Ulubelen et al.\textsuperscript{34}, studied the effect of diluents on the performance of phenytoin sodium capsules. Calcium sulphate dihydrate, lactose, maize starch, sodium sulphate were used as diluents. Colloidal silicon dioxide, magnesium stearate and talc were used as lubricants. Powder mixing and slugging affected the dissolution of phenytoin.

Chowhan and Ari\textsuperscript{35} studied the interaction of starch with ketorolac methamine in hard gelatin capsules. York\textsuperscript{14} reported that phenobarbitol sodium has no effect on dissolution if 50% lactose is used. Moisture content of starch was correlated with dissolution of drug.

Bell and Fell\textsuperscript{36} studied the effect of starch concentration on the release of phenobarbitone from hard gelatin capsules.
Davies and Fell\textsuperscript{37} studied the influence of starch and lactose on the release rates of drugs from hard gelatin capsules. Phenobarbitone (hydrophobic) and phenobarbitone sodium (hydrophilic) were filled in capsules. Dissolution testing was carried out by a beaker method. The presence of lactose and starch (at high level) influenced dissolution of hydrophobic drug but not the hydrophilic drug.

Newton et al.\textsuperscript{38}, demonstrated the use of lactose (upto 50\%) for poorly soluble drug like ethinamate. They concluded that the formulator should consider the solubility of filler as well as API while studying dissolution.

\textit{Disintegrants/superdisintegrants}

Desai et al.\textsuperscript{39}, have studied the effect of incorporating sodium starch glycollate, croscarmellose sodium or cross-linked polyvinylpyrolidone in hydrochlorthiazide capsules. The results of dissolution efficiency in 20 min revealed that fast flow lactose (45\%), hydrous lactose (25\%) and anhydrous lactose (10\%) decreased the drug dissolution after storage for 6 months at 50\textdegree C.

Dahl et al.\textsuperscript{40}, reported that use of disintegrants upto 10\% provides protection against stress due to high humidity. Six batches of hard gelatin capsules were manufactured to explore the effect of disintegrant level and capsular fill porosity on the dissolution behavior of encapsulated dosage forms after exposure to high humidity. The drug dissolution was faster from size ‘0’ capsule filled with 10 and 25\% disintegrant level, as compared to that from size ‘2’. The trend was reversed when identical products were exposed to high humidity but protected by polypropylene container/closure system.
Chowhan and Chi\textsuperscript{41} reported the effect of incorporation of ketorolac with crospovidone on the drug dissolution. Effect of particle size of drug, lubricant mixing time, powder properties, particle interactions were studied for dissolution. Scanning electron microscope was used to study interaction.

Botzolakis and Augsburger\textsuperscript{42} studied the role of disintegrants in hard gelatin capsules. The effect of machine forces and formulation content were studied on disintegration of hard gelatin capsules. Disintegration time was not always in rank order agreement with dissolution data. Three way ANOVA (4 drugs, 3 diluents and 2 levels) was carried out. More soluble filler required less amount of disintegrant.

Botzolakis et al.\textsuperscript{43}, compared the performance of various levels of newer disintegrants against 10% starch and 0% disintegrant as controls in dicalcium phosphate-based capsules filled on an instrumented Zanasi LZ-64 at a uniform compression force. In most cases, the dissolution rate of hydrochlorothiazide was dramatically enhanced. Disintegrant efficiency was concentration-dependent. Although the typical use levels of these disintegrants in tablets is 2-4\%, the most effective disintegrants required 4-6\% for fast dissolution. The importance of drug solubility or magnesium stearate level is also reported. When magnesium stearate was reduced (from 1 to 0.5\%) or when a more soluble drug (acetaminophen) was substituted for hydrochlorothiazide, less croscarmellose was needed to exert a similar effect on dissolution.

Ludwig and Van\textsuperscript{11,44} studied disintegration mechanism of hard gelatin capsules utilizing stereoscopic microscope and scanning electrone microscope. They also have evaluated the influence of the
composition of the test solutions on the disintegration of hard gelatin capsules.

Beecham Group Ltd.\textsuperscript{45} has been assigned patent on oral antibiotic-PVP capsules, with short disintegration times and rapid dissolution.

Ryder and Thomas\textsuperscript{46} studied the comparison of the effectiveness of several disintegrants in capsules of 4-ethoxycarbonylphenoxy-2'-pyridylmethane (BRL 10614).

\textit{Glidants/Lubricants/Surfactants}

Shimada Y et al.\textsuperscript{47}, measured adhesive forces between the particles in gelatin and HPMC capsules, containing corn starch, potato starch, lactose and glass beads, utilizing fine dedusting apparatus. Particles more than 10 \(\mu\)m size were removed by deduster. Potato starch in gelatin and corn starch in HPMC capsules showed high adhesiveness. There were higher amount of residue in gelatin than HPMC capsules.

Anno and Rees\textsuperscript{48} presented the paper on release of phenytoin sodium from capsules containing diluents, (calcium sulphate dihydrate, lactose) and lubricants such as magnesium stearate. The state of mixture was studied by scanning electron microscopy and X-ray analysis. The drug release was found to be dependent on type of excipient.

Botzolakis\textsuperscript{49} demonstrated enhanced liquid uptake into capsule plugs owing to surfactants. The most common surfactants employed in capsule formulations, are sodium lauryl sulfate and sodium
docusate. Levels of 0.1-0.5% are usually sufficient to overcome wetting problems.

Sadek et al.\textsuperscript{50}, reported that exceeding 0.25-0.5% of glidant worsen the flow of powder fill. Optimum concentration may be related to just coating the host particles. Exceeding this concentration will have no further improvement in flow. Glidants used were colloidal silica, corn starch, talc and magnesium stearate.

Stewart et al.\textsuperscript{51}, York\textsuperscript{52} and Augsburger and Shangraw\textsuperscript{53} have reported several possible mechanisms to improve the fluidity of powders by glidants such as colloidal silica, corn starch, talc and magnesium stearate.

Merle et al.\textsuperscript{54}, reported the influence on glidants on the dissolution rate of acetylsalicylic acid in hard gelatin capsules. Murthy and Samyn\textsuperscript{55} reported that increasing the concentration of hydrophobic lubricants, such as magnesium stearate, is generally understood to retard drug release by making formulations more hydrophobic. Temperli\textsuperscript{56} studied the effect of lubricants on filling of capsules, their stability at room temp.

Caldwell and Westlake\textsuperscript{57} reported the effect of incorporating water soluble lubricant such as magnesium lauryl sulfate on the release of lithium carbonate.

Newton et al.\textsuperscript{58}, reported the optimum use of lubricants. Increase in the concentration of hydrophobic lubricant such as magnesium stearate is generally understood to retard drug release by making formulation more hydrophobic by additional water repellent coating. Ethinimate was filled at high and low packing density. The
type, amount of excipient and applied pressure affected the drug release.

Processing

Podczeck and Newton\textsuperscript{59} have studied powder bulk characteristics and capsule filling performance on a tamp-filling machine with and without addition of various concentration of magnesium stearate. Magnesium stearate at a level of 0.8\% was not optimal for the processing.

Chowhan and Chi\textsuperscript{60-61} studied drug-excipient interaction resulting from powder mixing, role of disintegrants, lubricants on in vitro dissolution of prednisone and ketorolac tromethamine.

De Beukelaer and Van Ooteghem\textsuperscript{62} reported the influence of powder bed porosity and wettability on liquid penetration and on drug release of powder mixtures filled into hard gelatin capsules.

Elbary et al.\textsuperscript{63}, reported the dissolution rate of chlormaphenicol from hard gelatin capsules is a function of type of adjuvants and methods of granulation. Doelker et al.\textsuperscript{64}, studied the role of wetting on the release of hydrophobic drugs from hard gelatin capsules. Liquid diffusion through the wall and capillary penetration into the powder bed was studied. Effect of test medium and surfactant using falling bearing method was studied. The role of wetting agent, powder properties and particle size versus wetting characteristics were compared.
2.1.3 Disintegration, dissolution testing and conditions

Jones and Newton\textsuperscript{65} have reviewed disintegration testing on capsules. Polesuk\textsuperscript{66} studied the disintegration testing for hard gelatin capsules with different variables. Jones and Cole\textsuperscript{67} studied the influence of test conditions on disintegration time of gelatin capsules.

Jones and Newton\textsuperscript{68} have bibliographed dissolution methodology from 1974 to 1986. Khalil and Ali\textsuperscript{69} studied some formulation factors affecting disintegration and dissolution of chloramphenicol capsules. Lin S-L et al.\textsuperscript{70}, studied evaluation of various dissolution apparatus for capsules. Beaker and rotating basket USP were utilized, compared with variation in capsule holders. Diuretic and antidiabetic compounds were investigated by bead, plate, blade, holder and basket for disintegration test and proposed USP dissolution test. The influence of size of stirrer, volume of medium, size of screen cloth for making basket was studied and discussed.

\textit{Dissolution media}

Matthieu et al.\textsuperscript{71}, studied the influence of the solubility of excipients on the release of hydrophobic medicaments in hard gelatin capsules. Ludwig and Ooetgham\textsuperscript{11-12} reported that various filling principles themselves may be expected to influence drug release. This is particularly evident when the machines form the powder mass in the form of a compressed plug. hard gelatin capsules, when immersed in dissolution medium, they rupture first at thinnest shoulders portion. The degree of plug compaction can have a profound effect on drug release. The process of rupturing was observed by microscope. Hydrophilic and hydrophobic contents like aminophenazone,
phenacetin and copper sulphate filled in capsules. Measurement of solvent penetration was observed by scanning electron microscopy.

Boymond and Mathis\textsuperscript{72} studied the influence of the formulation on the release of ephedrine hydrochloride from hard gelatin capsules. Stirred flask method was utilized to study the effect on size, powder properties and effect of formulation with stability aspects. Release was delayed in case of hydrophobic excipients.

Newton and Bader\textsuperscript{73} studied the influence of drug and diluent particle size on the in vitro drug release from hard gelatin capsules. Lerk et al.\textsuperscript{74}, treated phenytoin with methylcellulose and compared the pure and treated drug plugs. The plugs were manually filled into hard gelatin capsules. The treated phenytoin dissolved and absorbed (in humans) considerably faster than the untreated drug. Bastami and Groves\textsuperscript{75} studied optimum particle size with surface/mass ratio and their effect on dissolution.

Geneidi et al.\textsuperscript{76}, developed solid dispersions of various drugs such as nitrofurantoin, ethotoin and coumarin with PEG-6000 and also prepared their co-precipitates with povidone-25000. Dissolution testing of API was carried out. Khalil and Ali\textsuperscript{77} studied the effect of dissolution medium and moisture content of the powder on the dissolution of chloramphenicol capsules.
2.2 Dissolution enhancement technologies for hydrophobic API fill

Chiou and Riegelman\textsuperscript{78} adopted solid dispersion to improve the solubility of drug. One or more active ingredient in an inert matrix in was prepared by fusion, solvent or melting-solvent method. Newton and Rowley\textsuperscript{79} studied the bed permeability of micronized ethinamate after granulating it and surprisingly the dissolution was greatly enhanced.

Samyn and Jung\textsuperscript{80} reported in vitro dissolution from several experimental capsule formulations. The influence of commonly used pharmaceutical excipients on disintegration and dissolution from experimental capsule formulations were studied. A low concentration of water soluble dye was incorporated to measure the dissolution in presence of hydrophobic excipients like dibasic calcium phosphate and magnesium stearate. FD & C Red No. 1 at 0.1\% level was used as a dye tracer. High and low pack density of fill, pH of medium and hydrophobicity of fillers played the role in dissolution behavior.
2.3 Shell modifications and drug release from hard capsules.

2.3.1 Patented Technologies

Rama Rao et al.\(^8^1\), used the glycine and citric acid approach added in the shell composition in order to prevent the cross-linking effect on gelatin capsule shells.

Adesunloye and Stach\(^8^2\) reported the synergistic use of glycine and citric acid in order to prevent or inhibit the cross-linking due to aldehydic group present by scavenging effect.

Noren et al.\(^8^3\), have assigned patent to Parke-Davis & Co. for capsule handling apparatus to produce capsules with holes in sides. Controulis et al.\(^8^4\), have assigned patent to Parke-Davis & Co. for utilizing hard gelatin capsules shell with perforated wall, having sealed holes, as a water-soluble package. Maddox\(^8^5\) has assigned a patent to Parke-Davis & Co. for perforated wall hard gelatin capsules containing soluble food extract.

2.3.2 Different shell materials

Eith et al.\(^8^6\), adopted injection molding process to prepare hard capsules made up of starch and compared its performance with gelatin.

Christen and Cheng\(^8^7\) assigned patent to DOW chemical company for method of manufacturing capsule shells for hydroxypropyl starches by dipping technique. Several polymers have been patented by plastic manufacturers to produce highly
thermoplastic films, made up of polyvinyl alcohol, copolymers of
vinyl pyrolidone, vinyl acetate, polymethylacrylates, polyoxethylene,
polyvinylalcohol esters etc.

Hoechst has registered a (BRD) patent for capsule shell
composition made up of copolymer polyethylene oxide, vinyl acetate,
v vinyl alcohol.

National starch and chemical corporation has utilized
modified starch for capsule production by dipping technique and has
registered a dutch patent.

Dow Chemical Company has been assigned a patent for dip
coating process for preparing hydroxyalkyl-cellulose ether film in
making hard capsules.

Tanabe Seiyaku Co. Ltd. has been assigned a patent for
capsules containing gelatin alkyl sulphate base. Manufacturing
method, standard properties, physical strength and solubility was
reported.

Langman has been assigned a patent for hydroxyalkyl-
cellulose ether capsules prepared by dip coating method. Thermal
gelation and means of heating moulds by induction was reported.

Greminger and Davis assigned to Dow chemical company for
the preparation of medicinal capsules from hydroxyalkyl-cellulose
ethers. Aqueous and non aqeous systems for manufacturing by
dipping method was used.
Dow Chemical Company\textsuperscript{94} has been assigned patent for preparation of medicinal capsule shells from hydroxyalkyl-alkyl cellulose esters.

Knox Gelatine Company Inc.\textsuperscript{95}, has been assigned patent for method of modifying Type A gelatin and product thereof. Gelatin films, gelatin modification, brittleness and drying rate were studied.

Greminger and Weaver\textsuperscript{96} have been assigned a patent for thermoplastic compositions of water-soluble cellulose ethers. Especially hydroxy propyl cellulose with ethyl glycol as plasticizer and triethyl citrate as modifier.

Murphy\textsuperscript{97} has been assigned a patent for methylcellulose capsules and process of manufacture. The moisture content of finished capsule was 2.5%. 5% sucrose or sorbitol were best choice for plasticizer. These capsules were not affected either in high humidity or by bacteria but they were poor in vitro dissolution.
2.4 References


64. Doelker E., Doelker C. and Mordier D. J. Pharm. Belg. 36: 404, 1981.