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DRUG DELIVERY SYSTEMS FOR THE ELDERLY:

Problems and Responses

M.K. Kottke, C.T. Rhodes, *L.T. Grady

Department of Pharmaceutics
University of Rhode Island, RI 02881-08091

*The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway, Rockville, MD 20852

CONTENTS:

OBJECTIVES

1. To review the various changes that can be observed as the body ages.
2. To explain how changes occurring in the elderly affect the administration of medication and its disposition within the body.
3. To outline factors that should be considered when designing drug delivery systems for the elderly.

1.0 INTRODUCTION

During the past few years, the pharmaceutical industry has become increasingly aware that the "elderly"

need to be considered as a population that, in some aspects, is separate and unique from the "adult" population. This is reflected most notably in the Food and Drug Administration's (FDA) Proposed Guideline for the Format and Content of the Clinical Section of an NDA which "specifically asks for analysis of data to look for age-related affects on safety and effectiveness" (1). Moreover, many package inserts now contain an additional section for geriatric patients under their caution listings. These changes are being made to accommodate the ever increasing proportion of elderly persons within our population. While many advances, such as those listed above, have been made by clinical researchers, formulators thus far have paid apparently little notice to the special needs that elderly patients have in terms of drug delivery systems. Certainly, there has been an ongoing search for systems that will deliver medication to patients with increased specificity and minimized side effects, but within the context of this paper, the term "drug delivery system" is defined to be a drug, in its final package, as it is supplied to the user. In other words, this paper focuses on the design of a system that will help the elderly overcome the various difficulties they experience when taking medication (e.g. difficulty swallowing, decreased manual dexterity).

1.1 Definition of Elderly

"Old Age" has been defined as the "advanced years of life when strength and vigor decline" (2). Although this definition appears to be quite ambiguous, one realizes

that it is necessarily so because the aging process itself is subject to a large amount of interindividual variation (3-6). This means that when comparing studies of a "young adult" population to studies of an "elderly" population, one will find the variance to be much greater in the elderly group. For instance, many readers probably know of a 65 year-old who "doesn't look a day past 50," while others may have made the acquaintance of a 50 year-old who is exceedingly frail.

1.1.1 Chronological Age

Due to this wide variation within the elderly population, it is difficult to devise a "catch-all" age one must attain to be considered elderly. Within the government, there also appears to be a problem of consistently defining this age group. Table 1, which lists a variety of federally funded programs and their corresponding age criteria, illustrates this point quite well. Table 2, lists what seems to be one of the better classification systems that has been devised (7). As well as being the system currently used by the US Bureau of the Census, it is often implemented in many studies that specifically deal with elderly populations (1,4)

1.1.2 Biological and Functional Age

In order to compensate for this wide variation that is noted among older populations, researchers have attempted to assess age in terms of biological or functional age. This basically involves combining a variety of factors together, such as physiological, psychological and intellectual parameters, to develop a

Table 1
Eligibility, by Age, for Federally Funded Programs

Age Criteria	Program
60	Older Americans Act Title VII
62	Housing and Urban Development
65	Medicare Program Title XVIII
70	Mandatory Retirement Age

Table 2
Commonly Utilized Age Classification System

Age	Category
65 - 74	Young-Old
75 - 84	Middle-Old
85 +	Old-Old

Source: Maddox GL. The Encyclopedia of Aging (1987)

"functional age" that would serve as the older counterpart of "developmental age" that is used when assessing neonatal development (5,6,8). The derivation of biological and functional age is quite complex and, while many interesting approaches to this problem have been studied, no one derivation has been universally accepted (5,8).

1.2 Demographics

Figure 1 gives a breakdown of the population as of the latest census in 1985. From this figure, it may be noted that the elderly really do not represent a major portion of our population. One may ask why this group has been the object of so much attention lately (9). The answer may be found in Figure 2, which illustrates the decennial percent increase among various portions of our

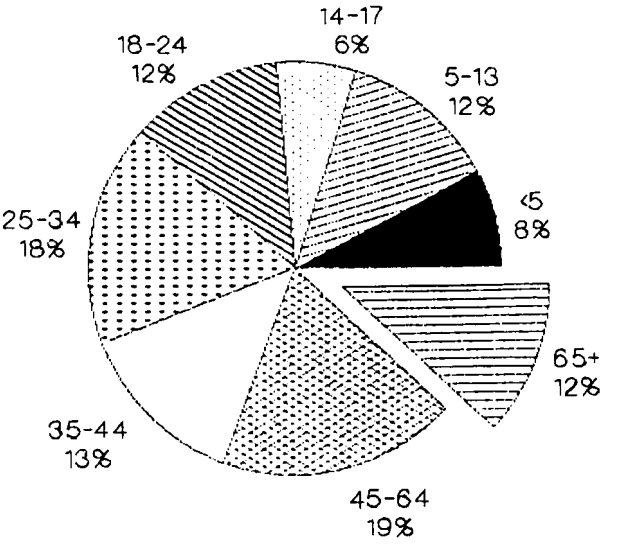


Figure 1.

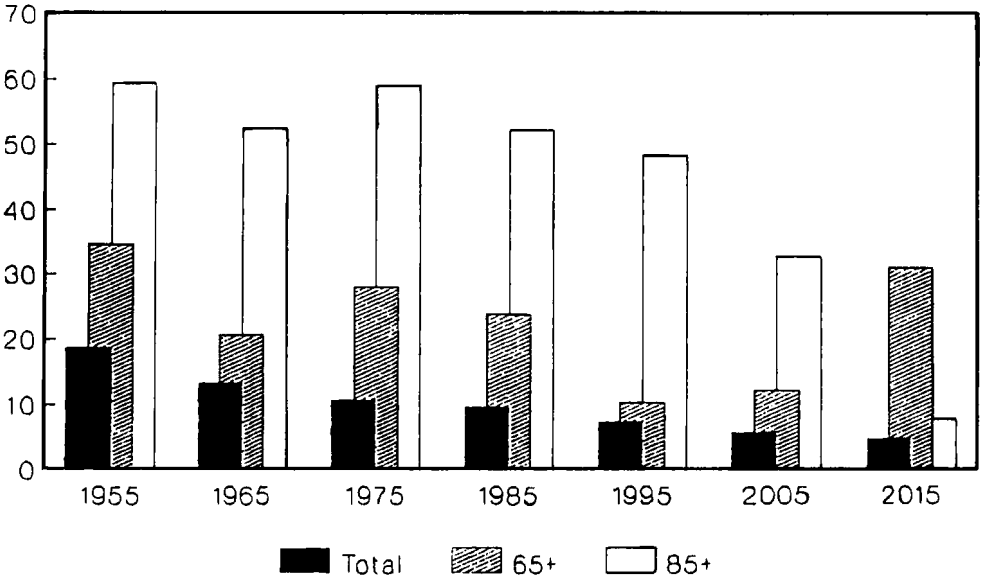


Figure 2.

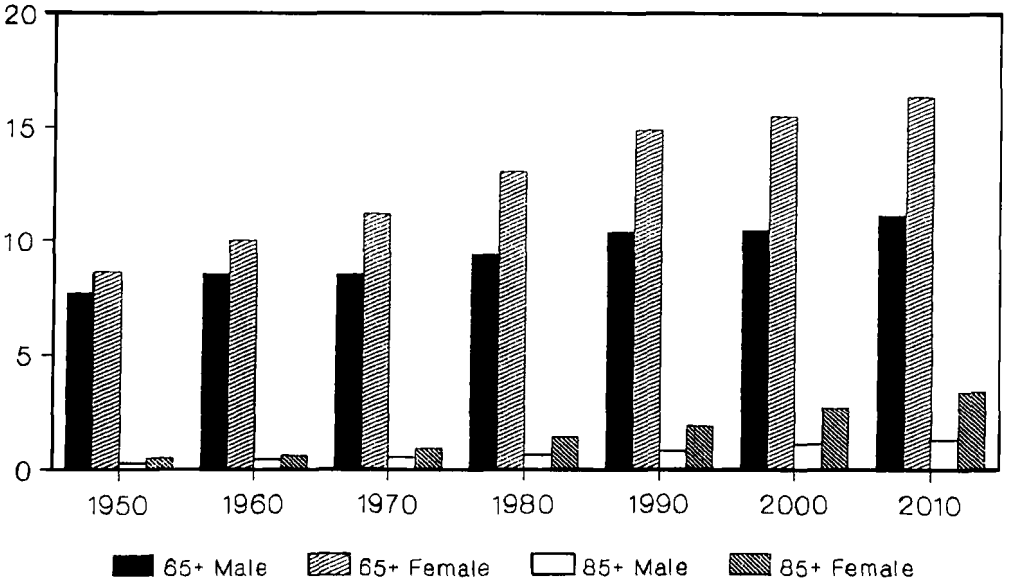


Figure 3.

population. One can see here that the growth rate among the elderly, most notably those over 85, far exceeds the growth of the population as a whole and will continue to do so into the 21st century (9). As depicted in Figure 3, this growth appears to be more prominent in females than in males, which may lead one to believe that these women will be living without the social or monetary support of their spouses. Indeed, latest census reports indicate that more than 28 percent of those over the age of 65 live alone (10). More importantly, in the same census report, it was determined that of those persons who are more than 65 years of age, over 15 percent live below the poverty level (10).

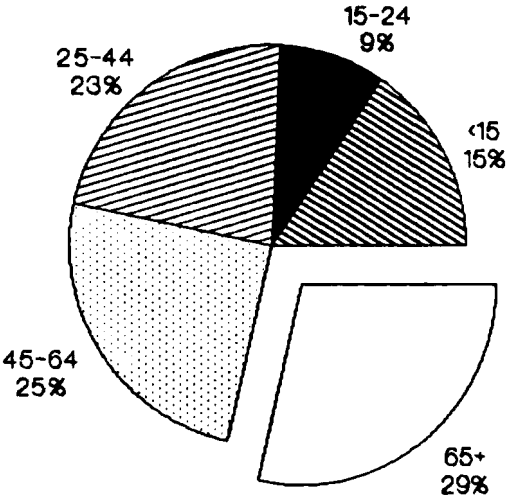


Figure 4.

2.0 DRUGS AND THE ELDERLY PATIENT

Within the medical community, it has been acknowledged that elderly patients often respond to drug therapy differently than their younger counterparts. Aside from alteration of various pharmacokinetic and pharmacodynamic processes, elderly patients tend to suffer from a number of chronic conditions and thus have more complex dosage regimens. Additionally, there are a variety of physical limitations prevalent amongst the elderly that may hinder their ability to self-administer medication.

2.1 Drug Use

Most of those involved in health care administration agree that elderly patients are the primary consumers of drug products. The actual extent to which this occurs is shown quite clearly in Figure 4. This figure gives an

Table 3
Prescription Drugs Commonly Used by Elderly Patients

Rank	Drug
1	Hydrochlorothiazide
2	Digoxin
3	Furosemide
4	Nitroglycerin
5	Potassium Chloride
6	Methyldopa
7	Ibuprofen
8	HCTZ-Triamterene
9	Prazosin
10	Oral Hypoglycemics

Source: Kurfees JF, Dotson RL. Drug interactions in the Elderly (1987)

analysis of the "drug mentions" in the US by age group (the term "drug mention" refers to those medications that have been "prescribed, recommended or given in any medical setting by a private physician") (11). As is shown in this figure, those over the age of 65, henceforth "the elderly", account for more than 28 percent of the drug mentions in the US. Thus, although the elderly only comprise 12 percent of our population, they are the biggest consumers of drug-related products (9,11).

2.1.1 Prescription

Table 3 lists ten prescription medications that are commonly used by elderly patients. These results were obtained from a study of 400 subjects over the age of 60 that was conducted in 1987 (12). Although the population studied was small, it was possible to evaluate use of medications that have come into use after 1985. This is an important consideration because most studies that have assessed the use of medication within larger populations

were conducted in or before 1985 and thus did not contain any medications that have been placed on the market since that time (12-18). Additionally, drug use based on therapeutic category (e.g. cardiovascular agents, hypoglycemics) is fairly consistent between the earlier studies and the study cited in this review (12-18).

2.1.2 OTC Drugs and Dietary Supplements

It is much more complicated to determine the use of over-the-counter drugs (OTC's), vitamins and dietary supplements by specific populations. This is due to a number of reasons: (1) these types of products can be purchased in places other than pharmacies which do not actively monitor drug-related purchases (e.g. supermarkets, convenience stores, gas stations); (2) often, the individual buying this type of product is not the ultimate user and (3) purchase does not preclude use (i.e. consumers who buy these products do not necessarily use them on a regular basis). Listed in Table 4 are some OTCs, vitamins and supplement products that are commonly used by elderly persons (19). Use is divided into two categories: (1) use by category therapeutic action and (2) use by product purchased). During the study referenced in this table, it was found that analgesics and antipyretics alone accounted for over 40 percent of the products used. In contrast to Table 3, the results included in Table 4 are from a large study (over 3000 patients) conducted in 1983 under a grant from the National Institute on Aging (NIA). As there have been no

Table 4
"OTC" Products Commonly Used by Elderly Patients

By Category	By Product
Analgesics & Antipyretics	*Aspirin
Multivitamins	Bufferin
Laxatives	Tylenol
Antacids	Anacin
Diet Supplements	Vitamin C
Cold Products	Metamucil
Antitussives	Vitamin E
Dermatologics	*Multivitamin
Miscellaneous	*Vitamin
	M-O-M

* Unspecified
Source: Wallace RB. Drug utilization in the rural elderly (1985)

major changes among the compounds used in these types of products since that time, this table is probably a fairly accurate representation of their use in the market today. Additionally, these results seem to concur with more recent studies that have been conducted in smaller populations (19-23).

2.2 Polypharmacy and Related Effects

Polypharmacy can be defined as the use of two or more therapeutic moieties by one patient. Because most elderly are subject to one or more chronic conditions (12,14,15,19,20,24), they are concurrently subject to polypharmacy and its related effects. Illustrated in Figure 5 are the number of drugs prescribed per physician visit as of 1985 in the US. While at least 55 percent of all patients, irrespective of age, are prescribed at least one medication per physician visit, elderly patients are much more frequently prescribed two or more medications

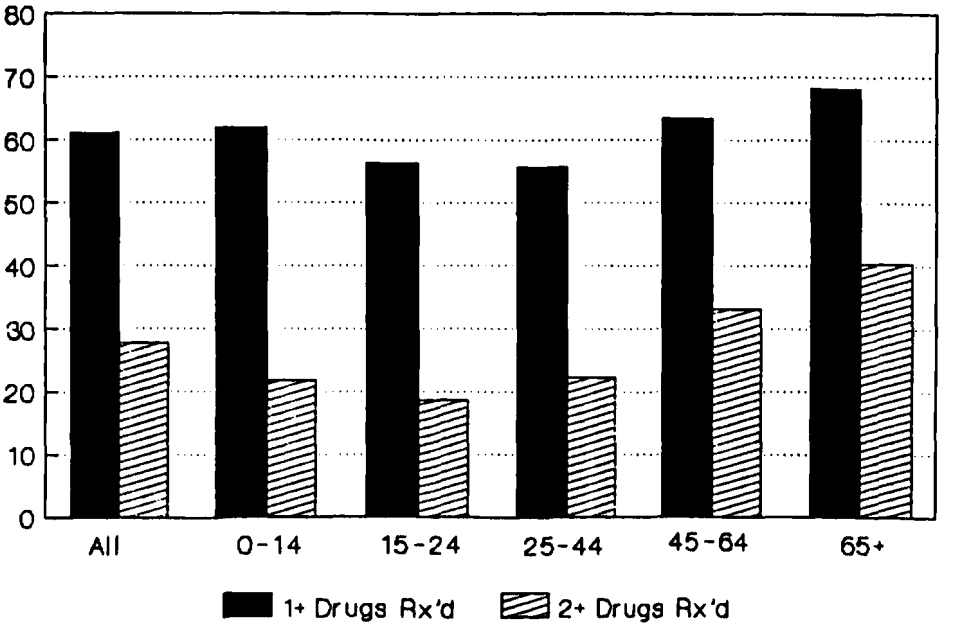


Figure 5.

(11). In fact, it has been found that the elderly commonly take anywhere from 2.6 to 4.5 medications per day (12,14,19,20,24). Moreover, increasing the number of medications prescribed results in more complex dosing regimens and an increased likelihood for adverse drug reactions (ADRs) (12,14,19,20,24-30). Some studies have even indicated that ADRs occur in 10 to 25 percent of all elderly patients taking medications (15,19). Of additional interest is the fact that digoxin and furosemide, which were found to be among the top ten prescriptions used by elderly patients (see Table 3), have been shown to account for more than 30 percent of all ADRs witnessed within the elderly population (12).

2.3 Effects of Aging on Drug Disposition

The effects of aging on drug disposition is one aspect of drug-taking behavior among the elderly that has been researched by individuals within both the medical and pharmaceutical fields. Before discussing the actual changes that occur with aging, two points must be stressed. First, due to the wide variation among older individuals that was previously discussed, it is very difficult to quantify the extent of changes that occur within this population. Secondly, most of these changes are related to the fact that with increasing age, there is an overall decrease in the capacity of homeostatic mechanisms to respond to physiological changes.

2.3.1 Pharmacokinetics

During the past decade, numerous articles reviewing the effects of aging on pharmacokinetic processes (i.e. absorption, distribution, metabolism and elimination) have been published (16,31-40). An outline of the observations made in these reports is supplied in Table 5. The absorption process is the only process that will be covered in depth within this article because this is the process that can most easily be manipulated through formulation techniques.

First of all, there is a decrease in gastric secretion which causes the elevated pH that has been observed in elderly patients (31-36,41,42). This condition is commonly referred to as hypochlorhydria or, in severe cases, achlorhydria, and may be the result of atrophic gastritis (38,41,42,43). It may have a

Table 5
Changes in Pharmacokinetic Processes that are Observed with Aging

Process	Changes	Effects
Absorption	↓Intestinal Blood Flow ↑Gastric pH ↓Active Absorption ↓GER ?	↓Rate of Absorption
Distribution	↓Cardiac Output ↑Fat:Lean Body Mass ↓Serum Albumin Conc.	↓Vd Water Sol. Drugs ↑Vd Lipid Sol. Drugs ↑Vd Protein Bd. Drugs
Metabolism	↓Hepatic Blood Flow ↓Liver Size ↓Phase I Metabolism ↑Incidence Liver Dysfunction	↑Half-Life Hepatically Extracted Drugs
Elimination	↓Renal Blood Flow ↓GFR ↓ARTS ↓Functioning Nephrons	↑Half-Life Renally Excreted Drugs

* Abbreviations: GER - Gastric Emptying Rate
Vd - Volume of Distribution
GFR - Glomerular Filtration Rate
ARTS - Active Renal Tubular Secretion

substantial effect on a formulation if an enteric-coated product or a weakly acidic or weakly basic drug is being considered. In the former case, the increased pH may cause the contents of the formulation to be prematurely released in the stomach, rather than in the small intestine and may lead to excessive gastrointestinal (GI) irritation. The elevated pH that exists within the stomach may also result in incomplete absorption of weakly acidic compounds from the stomach and decreased rate of absorption of poorly soluble weak bases.

The reduced gastric blood flow that has been noted in elderly patients may hinder the rate of absorption

(31,32,38,41,42). In most instances, this decrease in the rate of absorption does not necessarily cause a decrease in the extent of absorption. In fact, only those compounds that are actively absorbed (e.g. riboflavin) or are degraded within the stomach media (e.g. Vitamin B_{12}) have been shown to have a decreased extent of absorption (41,43).

There appears to be an ongoing dispute as to whether or not gastric emptying rate (GER) and GI motility are affected by aging (30-32,39,41,44-48). Most studies tend to suggest that there is, indeed, a decrease in GER as the body ages. As GER is the primary physiological determinant of the rate of absorption, one can see that a decrease in GER will result in a subsequent decreased rate of absorption, especially when coupled with the compromised blood flow also noted in elderly patients. Additionally, unpredictable GER has a significant impact on extended-release formulations as it becomes difficult to predict whether or not acceptable blood levels will be obtained (38). To circumvent the possible problems that may arise due to a decrease in GER, a liquid or readily disintegrating formulation may be used.

2.3.2 Pharmacodynamics

Although there are a number of reviews assessing the changes in pharmacodynamics that are prevailing in the elderly, this area has not been as widely studied as those changes occurring in pharmacokinetic processes (16,31,32,34,36). In Table 6, some of the major changes that have been evaluated in elderly patients are listed.

Table 6
Pharmacodynamic Changes Observed with Aging

Decrease Baroreflex Sensitivity
Decrease β-1 Receptor Response
Decrease α-2 Receptor Response
Increase Sensitivity to Barbiturates
Decrease Glucose Tolerance

The decrease in the ability of the aging body to respond to baroreflexive stimuli can result in very serious consequences for elderly patients (16,31,32). Due to this decrease in sensitivity and the decreased cardiac output witnessed in elderly patients, they are predisposed to the effects of orthostatic hypotension that can occur when one is taking antihypertensive medication (e.g. prazosin). Indeed, the fact that elderly persons are prone to accidental falls may be due to this change in sensitivity (16,31,32).

Decreases in β-1 receptor response were investigated when it was found that elderly patients taking beta-blockers (e.g. propranolol) were experiencing the ADRs associated with these medications but they were not obtaining the proper therapeutic response (i.e. decrease in heart rate) (16,31,32). Whether the exact mechanism for this decreased response is due to a decrease in affinity or a decrease in the number of receptors has yet to be conclusively determined (16).

The changes in α-2 receptor response observed in some elderly patients have not yet been found to have any clinical significance. Theoretically, this decrease

Table 7
Changes in and About the Oral Cavity Observed with Aging

Mucosa	Drier Increase Susceptibility to Injury Decrease Capillary Blood Supply
Muscle	Decrease Bulk and Tone Decrease Masticatory Efficiency
Salivary Glands	Decrease Resting Secretory Rate Increase Viscosity of Saliva Decrease Enzyme Activity of Saliva
Miscellaneous	Decrease Number of Taste Buds Increase Dysfunction and Cancer

should result in an increase in the amount of norepinephrine being released from nerve terminals, but this has not yet been demonstrated (16,31).

The incidence of diabetes and decreased glucose tolerance among the elderly is well documented (18,31,60,62). Due to this occurrence, formulators should make every attempt to avoid using any sugar-containing excipients in their production processes.

2.3.3 Absorption Within the Oral Cavity

When dealing with oral dosage forms it is important to study the various changes occurring within the oral cavity, particularly if a buccal or sublingual formulation is being considered. Table 7 lists the changes within the oral cavity that have thus far been elucidated (39,42,48-54). It is very important to note that there is a decrease in the capillary blood supply to the oral mucosa. Therefore, it may be difficult to predict accurately the absorption rates that will occur with

Table 8
Changes in Skin Characteristics Observed with Aging

Dry Skin
Loss of Elasticity
Impaired Wound Healing
Deletion and Derangement of
Small Blood Vessels
Increase Permeation to Water and
Some Chemicals
Decrease Clearance into Blood Stream
Decrease Absorption ?

sublingual and buccal formulations in the elderly age group. Additional changes occurring in and about the oral cavity will be discussed at length in another section of this review.

2.3.4 Percutaneous Absorption

With the increasing acceptance of transdermal formulations by the pharmaceutical industry and the trend towards an aging population that is occurring in our nation, it is vital that the effects of aging on percutaneous absorption be evaluated. Certainly, elderly patients are the primary users of such transdermal drug delivery systems (e.g. Transderm Nitro, Ciba-Geigy; Nitro Dur II, Key), so the need for assessment of percutaneous absorption in the elderly should be emphasized. In light of this, it is surprising to find that there have been relatively few studies published that specifically address percutaneous absorption in the elderly (55,56). Table 8 provides an outline of changes in characteristics of the skin that have been observed to occur with aging (55-58).

Table 9
Top Ten Chronic Conditions Among the Elderly

Rank	65 - 74	75 +
1	Arthritis	Arthritis
2	Hypertension	Hypertension
3	Heart Disease	Hearing Impair.
4	Hearing Impair.	Heart Disease
5	Orthopedic Impair.	Cataracts
6	Chronic Sinusitis	Orthopedic Impair.
7	Diabetes	Chronic Sinusitis
8	Cataracts	Visual Impair.
9	Tinnitus	Hardening of Art.
10	Hemorrhoids	Constipation

Source: Collins JG. Advancedata No. 155 (1988)

Researchers assessing the various factors surrounding percutaneous absorption (e.g. permeation, clearance) have theorized that although there is an increase in the rate of permeation through aging skin, substances that permeate through the skin have a slower rate of removal into the general circulation and thus distribution be incomplete (55,57). Unfortunately, there appear to be few published reports addressing this phenomena. Studies that do specifically evaluate percutaneous absorption have only used only one compound, testosterone, in their procedures (55,56). Therefore, prior to formulating drugs for transdermal delivery in the elderly, changes in percutaneous absorption that occur on aging should be assessed further.

2.4 Physical Limitations

Table 9 lists the top ten chronic conditions prevailing in the elderly population (59). Many of these conditions severely limit the range of activities that one

Figure 6.

can perform (see Figure 6) (60). Indeed, researchers have studied in depth the extent to which age limits one's activities of daily living (ADL) (18,62,63,64). Moreover, some of these conditions, such as arthritis and impaired vision, impinge upon the patient's ability to accurately self-administer medication.

2.4.1 Dexterity

Dexterity may be impaired in the elderly for a variety of reasons, such as the following: (1) over 45 percent of the elderly from some form of arthritis (59); (2) many elderly experience tremors associated with Parkinsonism or other neurological disorders and (3) frailty and weakness are prevalent in many elderly patients. In fact, the NIA has been conducting a comprehensive study to assess all of the characteristics

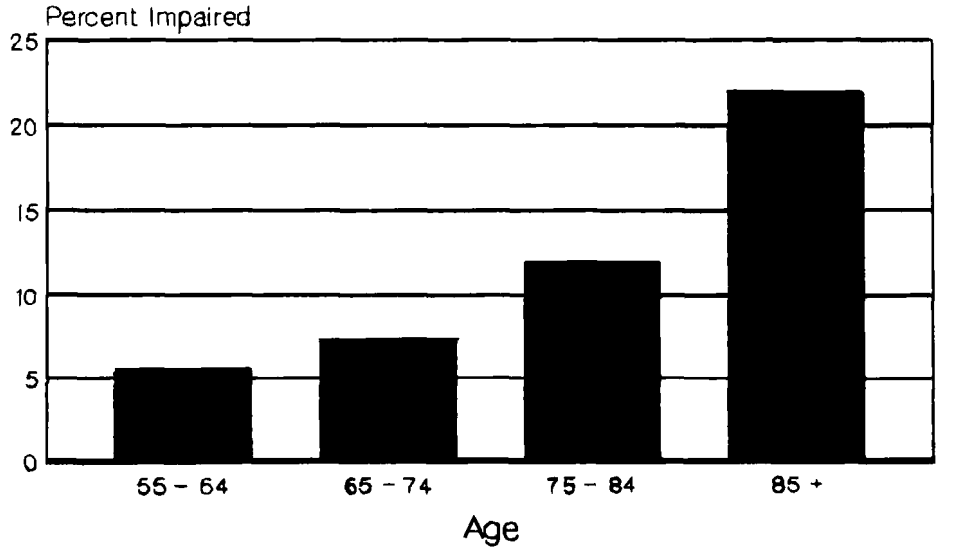


Figure 7.

common among the elderly. This study reveals that at least 13 percent of the elderly have some difficulty in handling small objects (e.g. tablets) (61). Another government study reports that more than 4 percent of the elderly experience difficulty preparing their own meals and therefore may encounter problems when self-administering medication (60).

2.4.2 Vision

Many people experience visual decline as they age (see Figure 7) (60). Impaired vision may also hinder one's ability to self-administer medication. Listed in Table 10 are some of the effects that are associated with impaired vision in the elderly. Some of the processes of self-administration upon which impaired vision in the

Table 10
Some Visual Declines Observed with Aging

General Acuity
Peripheral Vision
Ability to See in Low Light Levels
Ability to See Highly Reflective Surfaces in Bright Light
Ability to Discriminate Colors
Ability to Adapt to Darkness

elderly may impact are as follows: (1) the ability to accurately measure liquids; (2) the ability to correctly read instructions and (3) the ability to differentiate between various types of medications (both the labelling of these drugs and their physical characteristics) (62,65-67).

2.4.3 Taste

Changes in elderly patients' abilities to taste various substances do not necessarily effect the ease or difficulty of administration of medications, but these changes do have an impact on the patients' acceptance of a product. For instance, while it may be easier for patients to swallow liquid medications, they may find the taste or smell of these drugs so objectionable that they will refuse to take any medication prepared in this manner. Indeed, even some solid dosage forms carry with them objectionable tastes or odors that result in limitation of patient acceptance. Although there have been few studies assessing elderly patients' preference for taste, these reports have indicated that differences do exist between elderly and young adult populations

(42,48,49,68,69). It has been determined that although the number of taste buds declines with age, thresholds for certain tastes are affected while others are not. Unfortunately, reports of taste threshold changes among the elderly are contradictory, and it is difficult to ascertain what changes really do occur (42,48,49,68,69). Current reports claim that these changes in taste thresholds are not due to age, per se, but to medications the patient is taking (49,69). For example, it appears that medication ingestion elevates the sour threshold so that an increased concentration of sour compounds must exist for it to be detected in any patient taking medication (69).

2.4.4 Swallowing and Chewing

In addition to those changes occurring in the oral cavity (see Table 7), there are other factors that may inhibit an elderly patient's ability to both swallow and chew. For instance, xerostomia, or dry mouth, is a condition that is prevalent among older people. Xerostomia may be caused by any one of the following conditions: (1) elderly patients often do not consume adequate amounts of liquid and are thus dehydrated; (2) many elderly patients "mouth breathe" due to asthma or other respiratory diseases and (3) elderly patients often take medications having anticholinergic side effects (e.g. anitidepressants and neuroleptics) (28,53,54,71,72). Patients experiencing xerostomia often have difficulty swallowing tablets or capsules because they tend to adhere to the esophageal mucosa when it is dry (39,42,73-76). In

addition, esophageal lesions are common among the elderly and may affect a patient's ability to swallow due to inhibition of peristalsis by the weakened esophageal musculature (30,42).

The ability of elderly patients to chew has also been found to be compromised (42,49,50,55), perhaps as a result of the decreased bulk and tone of the oral musculature as one ages (55). Additionally, it has been estimated that 50 percent of all elderly persons in the US are fullly edentulous (i.e. toothless) (42,50). The absence of teeth not only hinders one's ability to chew, but also changes the bacterial flora within the oral cavity from predominately anaerobic to aerobic (42).

3.0 DIFFICULTIES ELDERLY PATIENTS MAY EXPERIENCE WITH EXISTING DRUG DELIVERY SYSTEMS

The changes expericenced in aging may affect a patient's ability to use some of the existing drug delivery systems. It should be kept in mind that, within the context of this review, a drug delivery system is not merely a novel dosage form. It is the dosage form with its container and labeling and any other items supplied with the medication to the user.

3.1 Compliance

One of the major difficulties elderly patients encounter while taking medication is the ability to comply with their prescribed dosage regimen. In fact, non-compliance among the elderly has been reviewed in numerous articles (23,31,34,37,77-85). A summary of the reasons why elderly patients are apt to be non-compliant is listed in Table 11.

Table 11
Possible Reasons for Non-Compliance Among the Elderly

Complex Dosage Regimen
Failure to Understand Directions
Impaired Vision
Confusion or Poor Memory
Unsuitable Packaging and Labeling
Cost of Medication
Emotional or Psychological Barrier

3.1.1 Complicated Dosing Schedules

As more than 40 percent of the elderly take two or more drugs on a regular basis, their dosage regimens tend to become complex (see Figure 5) (11,12,14,19,24). Not only may a patient be taking an increased number of medications, but often each medication must be taken in a different manner. Moreover, many elderly patients become easily confused or have failing memories. This is not necessarily an effect of aging, per se, but may be the effect of chronic conditions experienced by the elderly or even an adverse reaction associated with the medication a patient is taking. Nevertheless, the confusion some elderly patients may experience tends to make complicated dosing schedules even more difficult to follow. In order to bypass the problem of remembering when to take each particular medication, some patients may take all of the doses at the same time, which may result in the incidence of severe drug-drug interactions between medications (12,14,19,24). Even worse, are the cases when patients do not take their medications at all because they become too aggravated by the dosing schedules.

3.1.2 Inadequate Instructions

Non-compliance among elderly patients may also be attributable to a lack of adequate instructions to facilitate the proper administration of the medication(s). Pharmaceutical companies, pharmacists and physicians must all play a part in ensuring that patients receive clear instructions about taking the proper doses of medication at the correct time. Health care professionals may be taking for granted many factors associated with drug administration that are not apparent to the layman. Many patients may simply take the directions written on a medication label at face value. If, for example, the instructions state "Take one three times a day with meals," confusion may result because: (1) as is often the case among the elderly, a patient may not be consuming three meals a day and thus may only take two doses of the medication if he or she is dining twice a day; (2) a patient may take a medication three times a day and with each meal so that he or she is receiving six, not three, doses of medication or (3) a patient may be unsure about whether to take a medication before, after, or during a meal. Health care professionals, especially pharmacists, are obligated to ensure that all patients fully understand their prescribed dosing regimen so that non-compliance can be kept to a minimum (84,85).

3.1.3 Cost

The relatively high cost of many drugs often limits a patient's ability to obtain all the medications required for optimal health. It must be remembered that,

the elderly are not only the primary consumers of drug products but they are also a group that has a disproportionately high poverty level (over 15 percent) (9-11). Additionally, only those patients eligible for Medicaid have the opportunity for federal reimbursement of their medication expenditures (87,88). Fortunately, there are some state-level programs which provide funding for prescription medication to those patients who are economically depressed (89). However, these programs, both state and federal, usually do not cover the costs of any OTC products purchased by patients (87-89). It is imperative, therefore, that costs be minimized as much as possible so that these patients are able to purchase all medications necessary without undue financial strain.

3.1.4 Product Package and Label

A well known problem which elderly patients encounter with existing drug delivery systems is the ability to open the product's container or read the attached label (23,34,65-68,78,80-85,90,91). In fact, it is understood that the FDA has supplied three universities in the US with grants to assess the specific problems that elderly patients encounter with child-resistant containers (CRCs) and to devise a new type of CRC packaging that is both child-resistant and "elderly usable." One very unsettling practice that is often used by the elderly who are unable to handle CRC's is that they may leave the caps off medication bottles and thus promote product degradation. Or they may pour all of the medications into one, easily accessible bottle or even a dish. As a result, the

purpose of the CRC is defeated because any grandchild visiting has ready access to the medication. In addition, by pouring all contents into one jar, a patient no longer has a means for positively identifying each medication and its dosing schedule (85,90,91).

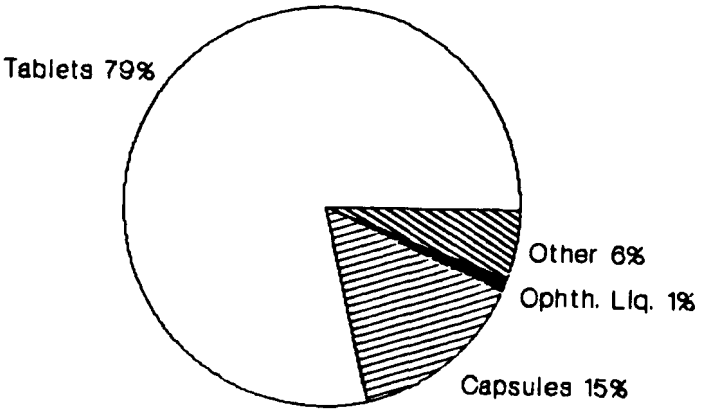
Printing that exists on the labels of many OTC products is so small that even those with "good" vision have difficulty reading them. When one is dealing with an elderly patient whose vision is impaired, it becomes obvious that this patient probably will not be able, or will make no attempt, to adequately read and follow the directions printed on a label. This problem is further compounded when there is poor contrast between the printing and the background of a lable. Moreover, elderly patients also may experience a decline in peripheral vision so that only those objects centered within the field of vision can be recognized (65-68).

3.2 Oral Dosage Forms

Solid oral dosage forms, particularly tablets, are the preferred type of formulation in the US. Not only are these products widely accepted by consumers, but they are also relatively cheaper to develop and manufacture than oral liquids, parenterals or suppositories. Figure 8 shows quite clearly that even the elderly primarily use solid oral dosage forms (19).

3.2.1 Chewable Tablets

It has already been noted that most elderly patients experience a decrease in their ability to chew efficiently



Source: Wallace, R.B. 1985

Figure 8.

(42,49,50,55). Therefore, by virtue of their design, chewable tablets are not often recommended for use by the elderly population (particularly those who are edentulous) (28,71,72,86). Most chewable formulations also rely upon an adequate amount of chewing action to obtain full release of their ingredients (e.g. chewing promotes the foaming action provided by some chewable antacid products). So, aside from being difficult for the elderly patient to use, full benefit of a chewable dosage form may not be achieved in older patients. Additionally, the use of chewable tablets by denture-wearers may cause irritation in their mouths (72).

3.2.2 Sublingual and Buccal Tablets

Although sublingual and buccal tablets (e.g. nitroglycerin, isosorbide) are used by a large number of

elderly patients, few if any, researchers have determined the effects that aging may have on the bioavailability of these dosage forms (48-54). Patient acceptance of these types of formulations must also be considered. Elderly patients who suffer from dry mouth conditions may find sublingual or buccal tablets irritating and may refuse to use such medications. Another problem may involve demented or contrary patients who may feel foreign objects inside their mouths and pull the tablets out before the active ingredients have been released from the formulation.

3.2.3 Capsules

A number of scientists have investigated the effect of formulation on esophageal transit and have found that capsules tend to adhere to the esophageal mucosa more often than any other oral dosage form (73-76). Moreover, due to the conditions of xerostomia and hindered swallowing that are prevalent among the elderly, mucosal adherence of capsules in these patients may be more pronounced (28,30,42,53,54,71,72). In light of these observations, the use of capsules by older patients may not be advisable. This is an extremely important consideration if the drug to be delivered is one that is known to cause esophageal ulceration (e.g. tetracycline, aspirin) (73).

3.2.4 Liquids

Most liquid formulations are not packaged in unit dosage form, therefore, prior to administration, the proper amount of medication to be taken for each dose must

be measured. This additional requirement may compound any difficulties a patient may have in following a prescribed schedule. Patients suffering from visual impairment, arthritis or tremors associated with neurologic disorders are particularly apt to become frustrated with this type of formulation. Visual impairments make it difficult, if not impossible, for many elderly patients to measure accurately the prescribed amounts of medication. Impaired dexterity, due to tremors or arthritis, may have effects on a patient's ability to hold both a spoon and a bottle at the same time while pouring out the desired amount of liquid.

Additional difficulties are encountered by elderly patients if a medication is in the form of a suspension. Problems may occur because a patient cannot see or disregards the words "Shake Well" on the label or is not able to exert the amount of agitation necessary to provide a uniform suspension. Certainly, unevenly distributed amounts of active ingredients throughout a suspension may result in serious consequences for a patient, either in terms of under- or over-dosing.

3.3 Transdermal Delivery Systems

While transdermal drug delivery may offer a means of increasing compliance among elderly patients, it has yet to be determined whether or not adequate bioavailability is provided to these patients in particular. Indeed, there may be a decrease in the absorption of compounds that are transdermally delivered to elderly patients (55-58). Still some may prefer the transdermal design and

Table 12
Possible Problems of Parenteral Delivery

Cost to Patient and Manufacturer
Patient Discomfort
Risk of Infection
Administration by Trained Personnel
Limitations on Particle Size
Sterilization Necessary
Prone to Chemical, Mechanical and Microbial Instability
Complex Manufacturing Processes
Cumbersome and Fragile Packaging

may opt to perform all the preliminary investigations necessary to quantify percutaneous bioavailability in older patients. If this route is chosen, one should keep in mind that transdermal products formulated around these changes are only applicable to the older patients, for whom the products have been designed. Such products will have differing release characteristics in the rest of the population. Therefore, these products, which will probably require lengthy preliminary studies, will only be used effectively by a limited portion of the population.

3.4 Parenteral Dosage Forms and Invasive Devices

Parenteral and invasive devices provide the distinct advantage of the delivery of medication directly into the bloodstream or at the site of action. Additionally, these methods result in certain patient compliance because, in most cases, an individual other than the patient is responsible for the administration of medication by these means. Unfortunately, this attribute is counteracted by numerous problems that are illustrated in Table 12.

In this table, it can be recognized that there are problems inherent in these types of formulations from both the patient's and the manufacturer's points of view. This is the reason why most pharmaceutical companies make attempts to avoid these types of dosages forms, if at all possible. However, with the advent of biotechnological products, which often do not lend themselves to "conventional" dosage formulations, parenteral and invasive measures may be the only answer.

4.0 ALTERNATIVE DELIVERY SYSTEMS

Although elderly patients seem to experience difficulties with those drug delivery systems listed above, other systems are currently available which may be more suited to the needs of these patients. While most of these systems are not specifically designed for the geriatric community, they may offer aid to this group of patients. This may be accomplished through the use of dosage formulations or packaging designs that are easier to handle or by supplying patients with devices or information which will enable them to better follow their prescribed dosing regimen.

4.1 Compliance Aids

Many pharmacists and physicians have recognized that most elderly patients have complicated dosing schedules and need some sort of reminder which will help them keep track of their prescribed regimens (23,31,71,72,76-85). This can be achieved through several methods. First, various types of packages, such as Dosett Trays, Calendar-Paks and Patient Med Paks, can be prepared by

pharmacists (78,81,90-92). These packages are usually devised so that all of the medications which have been prescribed at a specified time are packed together. For instance, all the medications which are to be taken before breakfast are placed in the same container, and all those to be taken one hour after breakfast are placed in another container. Labeling for each container should specify the time at which its contents are to be taken, as well as a list of each individual medication it holds. In an effort to promote this type of packaging, the United States Pharmacopeia (USP) has set guidelines for pharmacists to follow when preparing Patient Med Paks (92). In this manner, the USP has provided the pharmacist with a means to help out those patients with complex dosing schedules and still comply with official labeling criteria (i.e. it is not standard practice to supply more than one drug in a single container).

Another way in which pharmacists and physicians can help patients regulate their dosing schedules is by supplying them with drug reminder cards (31,78,83,84). The concept for the cards is essentially the same as that for the labels on the packaging described above (i.e. time of day and all medications to be taken at that time). Various modifications of this design can be made, such as including the physical characteristics of each medication or providing stickers to be placed on the card and on its corresponding container (i.e. one sticker is placed on the prescription bottle and the other sticker is placed next to the medication's name on the reminder card) (83,84).

Unfortunately, both the drug reminder cards and the packaging methods described above must be made for each patient on an individual basis, and some people are not willing to take the extra time needed to prepare these systems.

4.2 Oral Dosage Forms

The advantages of oral dosage formulations have already been discussed here. It appears that this route of drug delivery is preferred by physicians, patients and manufacturers alike (93-95). The relatively low cost of oral dosage forms makes them a particularly attractive means of drug delivery in those patients, such as the elderly, who may be economically depressed (10). These dosage forms are also comparatively easier to formulate, package and ship than other types of dosage forms (93-95). Moreover, changes in pharmacokinetic parameters among the elderly have only been assessed in those formulations which are oral or parenteral in nature (16,31-48). Therefore, it is appropriate to focus on oral dosage formulations for drug delivery in the elderly.

4.2.1 Granules

Granules are one type of oral formulation whose use among the elderly is warranted (86). This type of dosage form not only circumvents the difficulty in swallowing encountered, but also provides the patient with a certain amount of rehydration. As the elderly are often dehydrated, this is a feature which should not be overlooked. More importantly, medications which have been dispersed in a liquid are not likely to be affected by

decreases in gastric emptying rate that may occur in older patients.

Problems may still arise because granules may be supplied in either unit dose packages or in bulk containers. If unit dose packages are used, patients with impaired manual dexterity may have difficulty opening the packets. With bulk containers, most of the handling problems that were previously discussed about to liquid formulations can occur. But bulk containers do offer the advantage of dosage flexibility that cannot be realized with other solid dosage formulations.

4.2.2 Coated Tablets

Investigators studying the effects of dosage formulation on esophageal transit have concluded that coated tablets are less apt to adhere to the esophageal mucosa than other solid dosage forms (e.g. uncoated tablets, capsules) (72-76). In addition, this effect may be complemented by the use of oval shaped tablets, or what are commonly referred to as "caplets" (74-76). This type of tablet offers advantages over uncoated tablets and capsules, especially in those patients who have difficulty swallowing. However, it is imperative that physicians and pharmacists instruct patients to take their medication with a full glass of water because esophageal adherance is still possible in those patients who are dehydrated.

4.2.3 Effervescent Tablets

Effervescent tablets are another means of supplying medications to the elderly. This type of formulation provides the patient with an easy-to-swallow product which

is aesthetically pleasing (i.e. forms a clear solution rather than a cloudly suspension). However, pharmaceutical chemists are well aware of the problems that exist when preparing effervescent formulations. These problems may be solved, in part, by certain advances in pharmaceutical technology that allow for direct compression of all excipients (96-98). While this makes the manufacture of such products easier, stability problems still exist because these formulations must be adequately protected against moisture (93). As with granules, the type of packaging required for effervescent tablets can be a problem for those patients with impaired manual dexterity. Moreover, the sodium content necessary to manufacture this effervescent products may have serious implications when used by patients with hypertension or congestive heart failure.

4.2.4 Dispersible or Soluble Tablets

The trend towards formulation of dispersible tablets is evident in Europe (99). For example, it is understood that all tablets marketed in the Netherlands must have the ability to form an adequate dispersion when placed in water. In England, some non-steroidal anti-inflammatory drugs (NSAIDs), which are extensively used by arthritic patients, are now marketed as dispersible tablets.

A challenge faced by formulators designing dispersible tablets is the ability to develop a formulation that rapidly disintegrates and is able to withstand shipping processes. In addition, this type of tablet should form a uniform and somewhat stable

suspension when dispersed in water. An interesting answer to this challenge is the design of a "porous tablet" (100), in which a volatilizable solid (eg. urethane, ammonium bicarbonate) is added to a standard, directly compressible formulation. After the tablets have been compressed, the volatilizable solid is sublimed off by a freeze-drying process. The porous tablets produced are able to maintain their mechanical strength. As is the case with granules and effervescent tablets, dspersible tablets offer the patient a dosage form that is both portable and easy to swallow.

4.2.5 Tiltabs

Tiltab tablets represent one of the few dosage formulations that has been developed expressly to meet the needs of patients with impaired dexterity (101). Marketed by Smith, Kline & French Laboratories, Ltd. in several European countries, the novelty of the tiltab design is its irregular shape which prevents it from lying flat. Apparently, tablets manufactured in this fashion are easier to handle by those with impaired dexterity. Moreover, these tablets are readily identifiable by patients so that differentiation from other medication is facilitated. Other innovations like this are needed for drug delivery systems with the particular needs of the geriatric patient in mind.

4.2.6 Concentrated Oral Solutions

Presentation of a drug may be made in a solution of a concentration that allows doses of less than 5 ml (e.g. Intensol Concentrated Oral Solutions). This opens up another prospect for dosing the aged, infants or other

patients experiencing difficulties swallowing. Such preparations can be mixed with food or drink. Taste and solubility problems set limits on the number of successful formulations that may arise here. It should also be noted that small errors in the measurement of such preparations represent large mistakes in dosing (86).

5.0 FACTORS TO CONSIDER WHEN EVALUATING DRUG DELIVERY SYSTEMS FOR ELDERLY PATIENTS

After reviewing some methods which may be used to assist elderly patients in taking their medications, the specific characteristics desired in the design of drug delivery systems for these patients should be reviewed. For the sake of simplicity and practicality, discussion will be limited only to those factors involved in the design of dispersible solid dosage formulations.

5.1 Drug and Excipient Characteristics

Prior to the start of any formal laboratory work, the characteristics of the drug and excipients to be used must be considered. When performing this evaluation, it is necessary to keep in mind all of the pharmacokinetic and physical changes experienced by the elderly.

5.1.1 Particle Size

The relevance of particle size upon solid dosage formulations has been determined by a number of individuals (22,28,93-95,102-104). As is illustrated in Table 13, particle size affects the solid dosage formulation in numerous ways. For instance, particle size can have a profound effect on the dissolution of a formulation within the GI tract. This is most notably

Table 13
Processes in Solid Dosage Formulation Which are Affected by Particle Size

Disintegration
Dissolution
Gastrointestinal Bleeding
Flowability
Compressibility

characterized by the Noyes-Whitney equation in which

$$dM/dt = (D/h)S\ C_S - C$$

where: M = mass of drug dissolved

t = time

D = diffusion coefficient of drug

h = stationary layer thickness

S = effective surface area of drug particles

C_S = concentration of solution at saturation

C = concentration of solute at time t

As decreases in particle size produce increases in surface area (S), it becomes evident that particle size reduction provides an increase in the rate of dissolution (dM/dt). Remembering that elderly patients are likely to have decreased GER, one can see that increased dissolution rates are particularly desirable in these patients because once the formulation is in solution, GER is no longer able to limit significantly the rate of absorption (38,45,86,94,102).

Particle size has also been found to impact upon aspirin-induced GI blood loss (103,104). It has been

determined that GI microbleeding decreases as the particle size of the formulation declines (103,104). In theory, this occurs because the duration in which the aspirin particles are in contact with the GI mucosa is shortened as a result of the decreased particle size of formulation and subsequently, the increased rate of dissolution (22,93,103,104). Clearly then, based on the effects on dissolution and GI erosion, formulations with a smaller particle size are desired. However, if the particle size is too small, problems may arise in the handling of the powder during manufacture and its flow properties may be impeded leading to poor dosage uniformity (93,103,104).

5.1.2 pKa

As the acid content within the GI tract is known to change as the body ages, it is also important to evaluate the dissociation constant(s) (Ka) of the drug(s) which are to be used. From the Henderson-Hasselbach equation for weak acids where:

$$pH = pKa + \log (salt / acid)$$

it is apparent that changes in pH cause the proportions of drug which are ionized (salt) and unionized (acid) to change (102). Since most compounds dissolve more readily when they are in the ionized form, it can be theorized that conversion of drugs with poor solubility to their salt form facilitates their rate of dissolution. Indeed, Hoener & Benet have modified the Noyes-Whitney equation so that it includes the effects of pH and pKa upon the rate

of dissolution (105). For weak bases this equation is defined as

$$dM/dt = (DS/h)(C_s(1 + H+/Ka) - C_g)$$

where: C_g = concentration of drug in GI tract

C_s = solubility of drug in stationary layer

H+ = H+ concentration in GI tract

Ka = dissociation constant of drug

This further serves to illustrate the fact that as pH increases, poorly soluble weak bases are more likely to exist in the unionized form and thus have a decreased rate of dissolution. Since gastric pH has been found to be elevated in most elderly patients, products containing weak bases that are meant to be used in this population, should be formulated with these changes in mind.

5.1.3 Stability

While not exclusively relevant to the design of drug delivery systems for the elderly, the stability of drug(s) and excipient(s) used within a formulation may have a dramatic impact on the final product. If there are instabilities inherent in the materials used in the formulation, these problems most often are translated to the final product. Instability may be physical, chemical or microbial in nature (93,95,102). When one is dealing with solid dosage forms, physical and chemical instabilities often occur. Instability may be due to decomposition of an active ingredient through hydrolysis or oxidation, or it may be a result of incompatabilities that exist between a drug and the excipients being used.

The use of materials that are polymorphic in nature (i.e. have more than one type of molecular orientation in the solid state) may also be the cause of instability within a formulation (e.g. dissolution and absorption rates differ among the various polymorphs of a material). Additionally, if drug-excipient interactions are not carefully evaluated, tablet hardening and an accompanying decreased rate of dissolution may result as the tablets age (e.g. dibasic calcium phosphate and ascorbic acid) (93,95,102).

5.1.4 Disintegration

To provide the rapid rate of disintegration that is required to achieve efficient dispersion from tablets, the addition of a disintegrating agent is necessary. Such agents enable a formulator to produce a tablet that will quickly disintegrate when placed in a liquid (93,95,102,106). In addition, the use of suspending agents or surfactants may be desired so that more stable suspensions can be formed. In choosing these agents, it should be remembered that most elderly patients are unable to handle large loads of sodium. Therefore, compounds such as sodium starch glycolate may be inappropriate for use by these patients.

5.1.5 Compressibility and Flow

In order to produce tablets which are uniform in weight and content and exhibit a certain degree of mechanical strength, one needs a mixture of powders with good flow properties, a minimum tendency for segregation and the ability to be compressed (93,95,102,106). To

achieve these ends, granulation with other excipients is often necessary.

Segregation can be minimized by ensuring that all particles within a mixture have approximately the same size and density (93,95). The flow of particles, however, is a bit more complex. On the one hand, mixtures of small granule size (~800 μm) have the propensity to produce tablets with minimal dosage variation. But, if the particle size becomes too small (< 10 μm), flow through an orifice (e.g. a tablet press hopper) becomes impaired because the cohesive forces between the particles are of the same magnitude as the gravitational forces being imparted on the powder bed (102). The restricted flow may be improved by the addition of glidants, such as magnesium stearate or talc, but most of these agents are hydrophobic and may impair a tablet's ability to disperse (93,95,102). Superfine, high molecular weight polyethylene glycols (PEGs), which are water soluble, have been proposed for use as lubricant/glidant in tablet formulation (96). PEGs then may provide the formulator with an agent that is both lubricating and hydrophilic and as such may be a viable choice for use in the formulation of dispersible tablets.

Another factor that impacts upon tablet formation is the ability, or inability, of powders to be compressed. The ability of materials to be compressed may be due to the following: (1) compression force; (2) particle size and (3) deformation processes (93). Obviously, by increasing the force of compression, one can, in theory, increase the mechanical strength of the compact. There is

some evidence that suggests that the strength of the tablet may be increased by using granulations of smaller particle size (93). Here again, this increased strength must be balanced with the ability of the powder bed to flow through a hopper. It has also been found that in order for suitable compacts to be formed, a material must exhibit a certain amount of plastic (i.e. permanent) deformation (93,95). Powders that undergo more elastic than plastic deformation will lose their structure upon ejection from the tablet die. Therefore, if one is using a material that does not undergo a significant amount of plastic deformation, additional processing steps are necessary so that a stable structure can be produced.

It becomes evident that a variety of factors need to be considered when designing tablet formulations. In addition, certain compromises between these parameters must be made because it is nearly impossible to meet all specifications with the same process variables.

5.1.6 Pharmacokinetics

The pharmacokinetics of each compound should be determined when one is deciding which drug candidates to use in designing formulations for the elderly (see Table 5). For instance, it is known that some medications have an increased half-life within the bodies of older adults, either because thess drugs undergo extensive hepatic metabolism (e.g. diazepam, verapamil, pentazocine) or because they are primarily excreted by the kidneys (e.g. lithium, aminoglycosides, digoxin) (16,31-36). In addition, drugs which are highly protein bound (e.g.

warfarin) may be the cause of serious adverse reactions among elderly patients due to the decreased concentration of serum albumin in these patients and the subsequent rise in circulating "free" drug (16,31-36). So, if the pharmacokinetic behavior of the drug is known to change in elderly patients, it may be wise to avoid such drugs or to adjust the dosage accordingly.

5.2 Dosage Form Characteristics

Once the active ingredient(s) to be formulated has been determined, the overall attributes of the dosage formulation need to be considered. Such qualities may include a product's physical appearance, its sodium and salt content and its release characteristics (controlled or immediate).

5.2.1 Salt and Sucrose Content

The increased incidences of glucose intolerance, congestive heart failure and hypertension among elderly patients make them particularly sensitive to levels of sucrose and sodium. Those involved in the manufacture of antacids are well apprised of this as they are required to carry a precautionary statement on the label of those products that contain more than 5 milliequivalents of sodium per dose (71,72,86). Additionally, when reviewing the various liquid preparations that are available in the OTC market today, one can see that many of these products are now sugar- and/or sodium-free. Indeed, decreased sodium and sugar levels are beneficial to the entire population. This would seem to suggest that every effort should be made to keep sodium and sucrose contents to an

absolute minimum in those products that are intended for use in older patients.

5.2.2 Taste, Smell, Shape and Color

While the physical attributes of a product - such as taste, smell, shape and color - will not adversely affect elderly patients, these characteristics may impact substantially upon product acceptance by this group. For instance, the physical appearance of the medication (i.e. shape and color), rather than its name, is most often used as a means of product identification by elderly patients (34,63,79,81). In addition, most people tend to lose the ability to discriminate between colors (e.g. red/green, pastels) as they age (63-66,107). Therefore, it may be appropriate to compensate for this deficit by avoiding the use of those colors which are difficult for these patients to distinguish.

As this discussion pertains to dispersible preparations, the taste and smell of the formulation are also important aspects to be evaluated. Patient compliance will probably be poor if a product has an exceptionally bad taste or smell (e.g. acetaminophen). Adverse tastes and smells may be masked through novel techniques such as: (1) complexation of the drug by cyclodextrins; (2) use of pro-drugs and (3) coating of drug particles in fluidized-bed driers. Additionally, changes in taste preferences by older patients should be assessed.

5.2.3 Extended or Immediate Release

The use of extended- versus immediate-release preparations in elderly patients is quite complex. On the

one hand, the use of extended-release products is believed to increase patient compliance by making the dosing regimen less complex. But the erratic behavior of the GI system in older patients makes the release of such formulations difficult to predict accurately (28,70,83). Moreover, as the half-lives of some drugs (e.g. those primarily excreted renally or metabolized hepatically) are increased as the body ages, the probability of these compounds accumulating and causing adverse reactions also increases. Therefore, extended- or immediate-release formulation should be considered on an individual basis for each drug.

5.3 Package and Label Design

One of the most important aspects of drug delivery design for the elderly is the presentation of the package and its label. If the patient is unable to open a package or cannot read a label properly, even the best dosage formulation design will be unsuccessful. For prescription medications the package design is difficult to control because the container supplied by the manufacturer is not necessarily the container in which the medicine will be dispensed by the pharmacist. But, pharmacist selection of special packaging is a prospect open to most drugs whenever elderly-friendly packaging is in hand. OTC products, in partial contrast, provide a manufacturer with the opportunity to make substantial changes in the design of packages and thier labels. When developing a design, it is important to always keep in mind that impaired dexterity and visual decline are prevalent among the

Table 14
Suggestions for Labels Designed to be Used by Elderly Patients

Avoid Pastels
Use Matte Surfaces to Minimize Glare
Light Colors on Dark Background are More Visible than Dark Colors on Light Background
Use Distinct Spacing Between Letters
Increase the Height and Thickness of the Letters
*Use Additional Labels Which Explain the Purpose of the Medication

*this type of label is required on drugs dispensed in Denmark

elderly. Listed below in Table 14 are some suggestions which may be usefuly when designing a product's label (23,65,66,76).

In terms of the package itself, it is difficult to devise a package that is both childproof/tamperproof and still able to be opened easily by someone with impaired dexterity. It has been suggested that packaging a medication in unit dose Calendar-Paks may increase patient compliance (82). The problem is that other studies have shown that most elderly patients encounter problems when attempting to open this type of packaging (blister packaging) (78,88). Additionally, this type of packaging (i.e. C-Paks and the like) for OTC products may be unacceptable to the Federal Trade Commission and FDA as it promotes the daily use of the product. So, it is apparent that that different types of packaging are needed depending on whether a drug is for OTC or prescription-only use.

6.0 CONCLUSIONS

In conclusion, it is evident that numerous conditions exist which separate the "elderly" from "young adults." Moreover, some of these conditions have a substantial impact on the use of drug delivery systems by elderly patients. With the ever increasing proportion of elderly patients in our population, it is surprising that relatively few special products are marketed to accommodate the needs of these patients in terms of drug delivery design.

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