INTRODUCTION

The formulation scientist in the generic industry has a demanding role when developing generic oral solid dosage forms that not only need to match innovator products within tight acceptance criteria but should also circumvent restrictive formulation patents, which makes it extremely challenging to achieve the desired generic product.

As the innovator companies come under increasing pressure from generic competition, it becomes important that valuable aspects of intellectual property acquired during the development of a specific drug product be sufficiently detailed to file a formulation patent. Their primary goal is to prevent, as far as possible, generic drug products from entering the market until after the benefits of basic patent coverage and subsequent formulation patent protection have been suitably exploited. Innovator companies may also file additional patents related to the synthetic process employed to produce the active pharmaceutical ingredient (API) [1], the specific crystal form (polymorph) [2], the formulation [3], and the combination of the drug with other active(s), which might provide synergistic benefits over the specific drug administered alone [4], specific "use" patents [5], and, of late, "pediatric exclusivity" [6].

Although the literature abounds with numerous drug-product formulations, both qualitative and quantitative, it is rather surprising that formulation scientists struggle in their quest to match the innovator product from a bioequivalence point of view, resulting in failed biostudies. Possible reasons for not being able to match the innovator may well lie in the nature of the API material used [7,8], the composition of the formulation with respect to the excipients used [9,10], and the manufacturing process employed, among others [11]. Table 4.1 lists the effects of excipients on the pharmacokinetic parameters of oral drug products, clearly indicating the effect that excipients may have on bioavailability and bioequivalence [12].

TABLE 4.1
Potential Effects of Excipients on Pharmacokinetic Parameters after Oral Administration

Excipients	Example	ka	tmax	AUC
Diluents	Microcrystalline cellulose	↑	↓	↑/–
Disintegrants	Sodium starch glycolate	↑	↓	↑/–
Enteric coat	Cellulose acetate pthalate	↓	↑	↓/–
Glidant	Talc	—	—	—
Lubricants	Magnesium stearate	↓/↑	↑	↓/–
Sustained-release agents	Methylcellulose, ethylcellulose	↓	↑	↓/–

In all cases, these effects may be concentration or drug dependent.
↑ = increase, ↓ = decrease, — = no effect.
ka = absorption rate, tmax = time to peak concentration, AUC = area under the plasma drug concentration time curve.

Source: Adapted from Shargel L, Yu Y, eds. *Biopharmaceutic Considerations in Drug Product Design. Applied Biopharmaceutics and Pharmacokinetics*. 4th ed. New York: McGraw-Hill, Chapter 6, 1999:137.