ORAL DRUG DOSAGE FORMS HAVING A DESIRED PK PROFILE AND METHODS OF DESIGNING AND PRODUCING THEREOF

TECHNICAL FIELD

[0001] The present disclosure, in some aspects, is directed to methods of designing an oral drug dosage form formulated and configured to have a desired pharmacokinetic profile. In other aspects, the present disclosure is directed to oral drug dosage forms having a desired pharmacokinetic profile, and methods of making, such as three-dimensional printing, such oral drug dosage forms.

BACKGROUND

[0002] The growing understanding of the mechanisms of drugs and reagents increasingly illustrates the importance of precision *in vivo* drug delivery to ensure optimized delivery in location, time, and amount, to achieve a desired pharmacokinetic profile for best use, efficacy, and safety of said drugs, drug candidates, and reagents. To achieve a desired pharmacokinetic profile, certain drugs and reagents may require, *e.g.*, complex release profiles and/or administration dosing regimen. However, such demands required often run counter to manufacturing constraints and ensuring proper use and patient compliance via simplicity of administration, *e.g.*, once-daily oral dosage forms or delivery systems. Additionally, the design of a drug dosage form capable of achieving a desired pharmacokinetic profile in an individual may not be readily obtained, even when based on such testing as *in vitro* release profile testing.

[0003] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

BRIEF SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual,

wherein the oral drug dosage form comprises a dosage unit comprising:

a first modulated-release (MR1) portion comprising the drug; and

a second modulated-release (MR2) portion comprising the drug,

the method comprising:

(a) obtaining a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual;

(b) obtaining a MR2 PK curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual; and

(c) determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on the MR1 PK curve and MR2 PK curve such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

[0003b] In another aspect of the present disclosure, there is provided a method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual,

wherein the oral drug dosage form comprises a dosage unit comprising:

a first modulated-release (MR1) portion comprising the drug; and

a second modulated-release (MR2) portion comprising the drug,

the method comprising:

determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual, and a MR2 PK curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

[0003c] In a further aspect of the present disclosure, there is provided a method of three-dimensional printing of an oral drug dosage form designed herein.

[0003d] In another aspect of the present disclosure, there is provided an oral drug dosage form produced by the method disclosed herein.

[0003e] In a further aspect of the present disclosure, there is provided an oral drug dosage form comprising a fixed amount of a drug formulated and configured to have a desired composite pharmacokinetic (PK) profile, the oral drug dosage form having two dosage units stacked back-to-back, wherein each dosage unit comprises:

an immediate-release (IR) portion comprising the drug, the IR portion having an immediate-release profile;

an extended release (ER) portion comprising the drug, the ER portion having an extended-release profile; and

a shell,

wherein the IR portion has a top surface and a bottom surface, wherein the ER portion has a top surface and a bottom surface, wherein the shell partially surrounds the IR portion and the ER portion, and wherein the shell is in direct contact with both the IR portion and the ER portion and leaves one surface of the IR portion and/or one surface of the ER portion exposed.

[0004] In some ~~aspect~~examples, the present disclosure provides a method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual, wherein the oral drug dosage form comprises a dosage unit comprising: a first modulated-release (MR1) portion comprising the drug; and a second modulated-release (MR2) portion comprising the drug, the method comprising: (a) obtaining a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual; (b) obtaining a MR2 PK

curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual; and (c) determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on the MR1 PK curve and MR2 PK curve such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

[0005] In another ~~aspect~~example, the present disclosure provides a method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual, wherein the oral drug dosage form comprises a dosage unit comprising: a first modulated-release (MR1) portion comprising the drug; and a second modulated-release (MR2) portion comprising the drug, the method comprising: determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual, and a MR2 PK curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

[0006] In some ~~embodiment~~examples, the method further comprises obtaining the MR2 PK curve of the MR2 precursor drug dosage form comprising the MR2 portion in the individual.

[0007] In some ~~embodiment~~examples, the method further comprises obtaining the MR1 PK curve of the MR1 precursor drug dosage form comprising the MR1 portion in the individual.

[0008] In some ~~embodiment~~examples, the individual is a human. In some ~~embodiment~~examples, the individual is selected from the group consisting of a dog, a rodent, a ferret, a pig, a guinea pig, a rabbit, and a non-human primate.

[0009] In some ~~embodiment~~examples, the drug has linear pharmacokinetics.

[0010] In some ~~embodiment~~examples, the MR1 portion is a MR1 layer. In some ~~embodiment~~examples, the MR2 portion is a MR2 layer.

[0011] In some ~~embodiment~~examples, the MR1 portion is an immediate-release (IR) portion, the IR portion having an immediate-release profile. In some ~~embodiment~~examples, the MR2 portion is an extended-release (ER) portion, the ER portion having an extended-release profile.

[0012] In some ~~embodiment~~examples, the MR1 portion is a first extended-release (ER) portion, the first ER portion having an extended-release profile, and the MR2 portion is a second extended-release (ER) portion, the second ER portion having an extended-release profile.

[0013] In some ~~embodiment~~examples, the MR1 portion and the MR2 portion are stacked on top of each other. In some ~~embodiment~~examples, the MR1 portion and the MR2 portion are positioned side-by-side with each other.

[0014] In some ~~embodiment~~examples, the MR1 portion and MR2 portion are partially surrounded by a shell, and wherein the shell has a slower dissolution rate than the ER portion. In some ~~embodiment~~examples, the shell is non-erodible.

[0015] In some ~~embodiment~~examples, the MR1 portion has a top surface and a bottom surface, wherein the MR2 portion has a top surface and a bottom surface, and wherein the shell is in direct contact with both the MR1 portion and the MR2 portion and leaves one surface of the MR1 portion and/or one surface of the MR2 portion exposed.

[0016] In some ~~embodiment~~examples, the MR1 portion is stacked on top of the MR2 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR1 portion is in direct contact with the top surface of the MR2 portion.

[0017] In some ~~embodiment~~examples, the dosage unit further comprises a third modulated-release (MR3) portion. In some ~~embodiment~~examples, the MR3 portion is an IR portion, the IR portion having an immediate-release profile. In some ~~embodiment~~examples, the MR3 portion is an ER portion, the ER portion having an extended-release profile. In some ~~embodiment~~examples, the MR3 portion has a top surface and a bottom surface, wherein the MR2 portion is stacked on top of the MR3 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR2 portion is in direct contact with the top surface of the MR3 portion.

[0018] In some ~~embodiment~~examples, the MR2 portion is stacked on top of the MR1 portion, and wherein the shell leaves only the top surface of the MR2 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR2 portion is in direct contact with the top surface of the MR1 portion.

[0019] In some ~~embodiment~~examples, the MR1 portion is stacked on top of the MR2 portion, and wherein the shell leaves the top surface of the MR1 portion and the bottom surface of the MR2 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR1 portion is in direct contact with the top surface of the MR2 portion. In some ~~embodiment~~examples, the shell is between the MR1

portion and the MR2 portion. In some ~~embodiment~~examples, the dosage unit further comprises an intermediate portion, wherein the intermediate portion is between the MR1 portion and the MR2 portion.

[0020] In some ~~embodiment~~examples, the MR1 portion and the MR2 portion are positioned side-by-side with each other, wherein the shell leaves the top surface of both the MR1 portion and the MR2 portion exposed. In some ~~embodiment~~examples, the MR1 portion has a side surface, wherein the MR2 portion has a side surface, and wherein the side surface of the MR1 portion is in directed contact with the side surface of the MR2 portion. In some ~~embodiment~~examples, the shell separates the MR1 portion and the MR2 portion. In some ~~embodiment~~examples, the dosage unit further comprises an intermediate portion, wherein the intermediate portion is between the MR1 portion and the MR2 portion.

[0021] In some ~~embodiment~~examples, the oral drug dosage form comprises two dosage units. In some ~~embodiment~~examples, the two dosage units are the same. In some ~~embodiment~~examples, the two dosage units are different. In some ~~embodiment~~examples, the two dosage units are stacked back-to-back. In some ~~embodiment~~examples, the two dosage units are separated by the shell. In some ~~embodiment~~examples, the two dosage units are separated by an intermediate portion.

[0022] In some ~~embodiment~~examples, at least 80% the MR1 portion erodes within about 60 minutes following administration of the oral drug dosage form to the individual. In some ~~embodiment~~examples, the MR1 portion comprises an erodible material.

[0023] In some ~~embodiment~~examples, the MR2 portion comprises an erodible material, and wherein the drug contained in the MR2 portion is released from the oral drug dosage form over a period of at least about 5 hours.

[0024] In some ~~embodiment~~examples, the desired composite PK profile is determined based on having an area under the curve (AUC) and C_{max} within an acceptable threshold of a reference PK curve of the drug. In some ~~embodiment~~examples, the desired composite PK profile is further determined based on having a t_{max} within an acceptable threshold of a reference PK curve of the drug.

[0025] In some ~~embodiment~~examples, the method comprises selecting one or more parameters for the MR2 portion to obtain a desired release profile of the drug from the MR2 portion. In some ~~embodiment~~examples, the one or more parameters is selected from the group consisting of: thickness, surface area, substrate erosion rate, and drug concentration in the MR2 portion.

[0026] In some ~~embodiment~~examples, the method further comprises determining the MR1 PK curve and the MR2 PK curve and adjusting the relative amounts of the drug in the MR1 portion and the MR2 portion.

[0027] In some ~~embodiment~~examples, the method further comprises determining a composite PK curve of the oral drug dosage form. In some ~~embodiment~~examples, the method further comprises adjusting the relative amounts of the drug in the MR1 portion and the MR2 portion based on a comparison of the composite PK curve and the desired composite PK profile.

[0028] In some ~~embodiment~~examples, the method further comprises producing the oral drug dosage form. In some ~~embodiment~~examples, the oral drug dosage form is produced by three-dimensional printing. In some ~~embodiment~~examples, the three-dimensional printing is carried out by fused deposition modeling (FDM). In some ~~embodiment~~examples, the three-dimensional printing is carried out by melt extrusion deposition (MED).

[0029] In another ~~aspect~~example, the present disclosure provides a method of three-dimensional printing of an oral drug dosage form designed according to any one of the methods described herein.

[0030] In another ~~aspect~~example, the present disclosure provides an oral drug dosage form produced by the methods described herein.

[0031] In another ~~aspect~~example, the present disclosure provides an oral drug dosage form comprising a fixed amount of a drug formulated and configured to have a desired composite pharmacokinetic (PK) profile, the oral drug dosage form having two dosage units stacked back-to-back, wherein each dosage unit comprises: a first modulated-release (MR1) portion comprising the drug; a second modulated-release (MR2) portion comprising the drug; and a shell, wherein the MR1 portion has a top surface and a bottom surface, wherein the MR2 portion has a top surface and a bottom surface, wherein the shell partially surrounds the MR1 portion and the MR2 portion, and wherein the shell is in direct contact with both the MR1 portion and the MR2 portion and leaves one surface of the MR1 portion and/or one surface of the MR2 portion exposed. In some ~~embodiment~~examples, the MR1 portion is an IR portion, the IR portion having an immediate-release profile, and the MR2 portion is an extended release (ER) portion comprising the drug, the ER portion having an extended-release profile. In some ~~embodiment~~examples, the MR1 portion is a first ER portion, the first ER portion having an extended-release profile, and the MR2 portion is a second extended release (ER) portion comprising the drug, the second ER portion having an extended-release profile. In some ~~embodiment~~examples, the drug

has linear pharmacokinetics. In some ~~embodiment~~examples, the shell is non-erodible. In some ~~embodiment~~examples, the MR1 portion and the MR2 portion are stacked on top of each other. In some ~~embodiment~~examples, the MR1 portion and the MR2 portion are positioned side-by-side with each other. In some ~~embodiment~~examples, at least in one of the dosage units, the MR1 portion is stacked on top of the MR2 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR1 portion is in direct contact with the top surface of the MR2 portion. In some ~~embodiment~~examples, the dosage unit further comprises a third modulated-release (MR3) portion. In some ~~embodiment~~examples, the MR3 portion is an IR portion. In some ~~embodiment~~examples, the MR3 portion is an ER portion. In some ~~embodiment~~examples, the MR3 portion is an IR portion, wherein the MR3 portion has a top surface and a bottom surface, wherein the MR2 portion is stacked on top of the MR3 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR2 portion is in direct contact with the top surface of the MR3 portion. In some ~~embodiment~~examples, at least in one of the dosage units, the MR2 portion is stacked on top of the MR1 portion, and wherein the shell leaves only the top surface of the MR2 portion exposed. In some ~~embodiment~~examples, the bottom surface of the MR2 portion is in direct contact with the top surface of the MR1 portion. In some ~~embodiment~~examples, at least in one of the dosage units, the MR1 portion and the MR2 portion are positioned side-by-side with each other, and wherein the shell leaves the top surface of both the MR1 portion and the MR2 portion exposed. In some ~~embodiment~~examples, the two dosage units are the same. In some ~~embodiment~~examples, the two dosage units are different. In some ~~embodiment~~examples, substantially all of the MR1 portion erodes within at least about 20 minutes following administration of the oral drug dosage form to an individual. In some ~~embodiment~~examples, the MR1 portion comprises an erodible material. In some ~~embodiment~~examples, the MR2 portion comprises an erodible material, and wherein the drug contained in the MR2 portion is released from the oral drug dosage form over a period of at least about 6 hours.

[0032] In another ~~aspect~~example, the present disclosure provides an oral drug dosage form comprising a fixed amount of a drug formulated and configured to have a desired composite pharmacokinetic (PK) profile, the oral drug dosage form having two dosage units stacked back-to-back, wherein each dosage unit comprises: an immediate-release (IR) portion comprising the drug, the IR portion having an immediate-release profile; an extended release (ER) portion comprising the drug, the ER portion having an extended-release profile; and a shell, wherein the IR portion has a top surface and

a bottom surface, wherein the ER portion has a top surface and a bottom surface, wherein the shell partially surrounds the IR portion and the ER portion, and wherein the shell is in direct contact with both the IR portion and the ER portion and leaves one surface of the IR portion and/or one surface of the ER portion exposed. In some ~~embodiment~~examples, the drug has linear pharmacokinetics. In some ~~embodiment~~examples, the shell is non-erodible. In some ~~embodiment~~examples, the IR portion and the ER portion are stacked on top of each other. In some ~~embodiment~~examples, the IR portion and the ER portion are positioned side-by-side with each other. In some ~~embodiment~~examples, at least in one of the dosage units, the IR portion is stacked on top of the ER portion, and wherein the shell leaves only the top surface of the IR portion exposed. In some ~~embodiment~~examples, the bottom surface of the IR portion is in direct contact with the top surface of the ER portion. In some ~~embodiment~~examples, the dosage unit further comprises a second IR portion, wherein the second IR portion has a top surface and a bottom surface, wherein the ER portion is stacked on top of the second IR portion, and wherein the shell leaves only the top surface of the IR portion exposed. In some ~~embodiment~~examples, the bottom surface of the ER portion is in direct contact with the top surface of the second IR portion. In some ~~embodiment~~examples, at least in one of the dosage units, the ER portion is stacked on top of the IR portion, and wherein the shell leaves only the top surface of the ER portion exposed. In some ~~embodiment~~examples, the bottom surface of the ER portion is in direct contact with the top surface of the IR portion. In some ~~embodiment~~examples, at least in one of the dosage units, the IR portion and the ER portion are positioned side-by-side with each other, and wherein the shell leaves the top surface of both the IR portion and the ER portion exposed. In some ~~embodiment~~examples, the two dosage units are the same. In some ~~embodiment~~examples, the two dosage units are different. In some ~~embodiment~~examples, substantially all of the IR portion erodes within at least about 20 minutes following administration of the oral drug dosage form to an individual. In some ~~embodiment~~examples, the IR portion comprises an erodible material. In some ~~embodiment~~examples, the ER portion comprises an erodible material, and wherein the drug contained in the ER portion is released from the oral drug dosage form over a period of at least about 6 hours.

[0033] It will also be understood by those skilled in the art that changes in the form and details of the implementations described herein may be made without departing from the scope of this present disclosure. In addition, although various advantages, aspects, examples and objects have been described with

reference to various implementations, the scope of this present disclosure should not be limited by reference to such advantages, aspects, examples and objects.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] **FIGS. 1A-1J** show exemplary dosage units and oral drug dosage forms.

[0035] **FIGS. 2A-2E** show deconstructed and deconstructed, cross-sectional views of exemplary dosage units and oral drug dosage forms.

[0036] **FIG. 3** is a schematic of an exemplary workflow of the 3D Printing Formulation by Design (3DPFbD®) approach.

[0037] **FIGS. 4A-4E** show schematics of an exemplary oral drug dosage form comprising an extended-release (ER) portion, an immediate-release (IR) portion, and a shell. **FIG. 4A** depicts a deconstructed view of the oral drug dosage form to show the individual components thereof. **FIG. 4B** depicts the assembled oral drug dosage form. **FIG. 4C** is a schematic showing dimensional aspects of the oral drug dosage form. **FIG. 4D** shows the compositions of the components of the oral drug dosage form. **FIG. 4E** is a cross-sectional view of the oral drug dosage form.

[0038] **FIG. 5** shows *in vivo* pharmacokinetic curves of an IR precursor drug dosage form and an IR reference drug dosage form.

[0039] **FIG. 6** shows an *in vivo* pharmacokinetic curve of an ER precursor drug dosage form.

[0040] **FIG. 7** shows theoretical simulated PK curves of oral drug dosage forms having different IR:ER drug ratios as compared to the PK curve of a reference drug.

[0041] **FIG. 8** shows *in vivo* pharmacokinetic curves of a whole oral drug dosage form having 100 mg of the drug, an IR reference drug dosage form having 50 mg of the drug, and an ER reference drug dosage form having 100 mg of the drug.

[0042] **FIG. 9** shows *in vitro* dissolution rates of a whole oral drug dosage form having 100 mg of the drug and an ER reference drug dosage form having 100 mg of the drug.

[0043] **FIG. 10** shows an *in vivo* pharmacokinetic curve of an optimized oral drug dosage form.

[0044] **FIG. 11** shows *in vivo* pharmacokinetic curves of an ER precursor drug dosage form having 100 mg of the drug and an ER reference drug dosage form having 100 mg of the drug.

[0045] **FIG. 12** shows *in vivo* pharmacokinetic curves of an optimized 3D-printed oral drug dosage form (100 mg of the drug), the theoretical prediction of the 3D-printed oral drug dosage

CLAIMS

What is claimed is:

1. A method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual,

wherein the oral drug dosage form comprises a dosage unit comprising:

a first modulated-release (MR1) portion comprising the drug; and

a second modulated-release (MR2) portion comprising the drug,

the method comprising:

(a) obtaining a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual;

(b) obtaining a MR2 PK curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual; and

(c) determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on the MR1 PK curve and MR2 PK curve such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

2. A method of designing an oral drug dosage form having a fixed amount of a drug and a desired composite pharmacokinetic (PK) profile in an individual,

wherein the oral drug dosage form comprises a dosage unit comprising:

a first modulated-release (MR1) portion comprising the drug; and

a second modulated-release (MR2) portion comprising the drug,

the method comprising:

determining the relative amounts of the drug in the MR1 portion and the MR2 portion based on a MR1 PK curve of a MR1 precursor drug dosage form comprising the MR1 portion in the individual, and a MR2 PK curve of a MR2 precursor drug dosage form comprising the MR2 portion in the individual such that the MR1 portion and the MR2 portion when combined together produce the oral drug dosage form having the desired composite PK profile in the individual.

3. The method of claim 2, further comprising obtaining the MR2 PK curve of the MR2 precursor drug dosage form comprising the MR2 portion in the individual.

4. The method of claim 2 or 3, further comprising obtaining the MR1 PK curve of the MR1 precursor drug dosage form comprising the MR1 portion in the individual.

5. The method of any one of claims 1-4, wherein the individual is a human.

6. The method of any one of claims 1-4, wherein the individual is selected from the group consisting of a dog, a rodent, a ferret, a pig, a guinea pig, a rabbit, and a non-human primate.

7. The method of any one of claims 1-6, wherein the drug has linear pharmacokinetics.

8. The method of any one of claims 1-7, wherein the MR1 portion is a MR1 layer.

9. The method of any one of claims 1-8, wherein the MR2 portion is a MR2 layer.

10. The method of any one of claims 1-9, wherein the MR1 portion is an immediate-release (IR) portion, the IR portion having an immediate-release profile.

11. The method of any one of claims 1-10, wherein the MR2 portion is an extended-release (ER) portion, the ER portion having an extended-release profile.

12. The method of any one of claims 1-9, wherein the MR1 portion is a first extended-release (ER) portion, the first ER portion having an extended-release profile, and wherein the MR2 portion is a second extended-release (ER) portion, the second ER portion having an extended-release profile.

13. The method of any one of claims 1-12, wherein the MR1 portion and the MR2 portion are stacked on top of each other.

14. The method of any one of claims 1-12, wherein the MR1 portion and the MR2 portion are positioned side-by-side with each other.

15. The method of claim 13 or 14, wherein the MR1 portion and MR2 portion are partially surrounded by a shell, and wherein the shell has a slower dissolution rate than the ER portion.

16. The method of claim 15, wherein the shell is non-erodible.

17. The method of claim 15 or 16, wherein the MR1 portion has a top surface and a bottom surface, wherein the MR2 portion has a top surface and a bottom surface, and wherein the shell is in direct contact with both the MR1 portion and the MR2 portion and leaves one surface of the MR1 portion and/or one surface of the MR2 portion exposed.

18. The method of claim 17, wherein the MR1 portion is stacked on top of the MR2 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed.

19. The method of claim 18, wherein the bottom surface of the MR1 portion is in direct contact with the top surface of the MR2 portion.

20. The method of claim 18 or 19, wherein the dosage unit further comprises a third modulated-release (MR3) portion, wherein the MR3 portion is an IR portion, the IR portion having an immediate-release profile.

21. The method of claim 20, wherein the MR3 portion has a top surface and a bottom surface, wherein the MR2 portion is stacked on top of the MR3 portion, and wherein the shell leaves only the top surface of the MR1 portion exposed.

22. The method of claim 21, wherein the bottom surface of the MR2 portion is in direct contact with the top surface of the MR3 portion.

23. The method of claim 17, wherein the MR2 portion is stacked on top of the MR1 portion, and wherein the shell leaves only the top surface of the MR2 portion exposed.

24. The method of claim 23, wherein the bottom surface of the MR2 portion is in direct contact with the top surface of the MR1 portion.

25. The method of claim 17, wherein the MR1 portion is stacked on top of the MR2 portion, and wherein the shell leaves the top surface of the MR1 portion and the bottom surface of the MR2 portion exposed.

26. The method of claim 25, wherein the bottom surface of the MR1 portion is in direct contact with the top surface of the MR2 portion.

27. The method of claim 25, wherein the shell is between the MR1 portion and the MR2 portion.

28. The method of claim 25, wherein the dosage unit further comprises an intermediate portion, wherein the intermediate portion is between the MR1 portion and the MR2 portion.

29. The method of claim 17, wherein the MR1 portion and the MR2 portion are positioned side-by-side with each other, wherein the shell leaves the top surface of both the MR1 portion and the MR2 portion exposed.

30. The method of claim 29, wherein the MR1 portion has a side surface, wherein the MR2 portion has a side surface, and wherein the side surface of the MR1 portion is in directed contact with the side surface of the MR2 portion.

31. The method of claim 29, wherein the shell separates the MR1 portion and the MR2 portion.

32. The method of claim 29, wherein the dosage unit further comprises an intermediate portion, wherein the intermediate portion is between the MR1 portion and the MR2 portion.

33. The method of any one of claims 1-32, wherein the oral drug dosage form comprises two dosage units.

34. The method of claim 33, wherein the two dosage units are the same.

35. The method of claim 33, wherein the two dosage units are different.

36. The method of any one of claims 33-35, wherein the two dosage units are stacked back-to-back.

37. The method of claim 36, wherein the two dosage units are separated by the shell.

38. The method of claim 36, wherein the two dosage units are separated by an intermediate portion.

39. The method of any one of claims 1-38, wherein at least 80% the MR1 portion erodes within about 60 minutes ~~following administration of~~ after the oral drug dosage form is to be administered to the individual.

40. The method of claim 29, wherein the MR1 portion comprises an erodible material.

41. The method of any one of claims 1-40, wherein the MR2 portion comprises an erodible material, and wherein the drug contained in the MR2 portion is released from the oral drug dosage form over a period of at least about 5 hours.

42. The method of any one of claims 1-41, wherein the desired composite PK profile is determined based on having an area under the curve (AUC) and C_{max} within an acceptable threshold of a reference PK curve of the drug.

43. The method of claim 42, wherein the desired composite PK profile is further determined based on having a t_{max} within an acceptable threshold of a reference PK curve of the drug.

44. The method of any one of claims 1-43, wherein the method comprises selecting one or more parameters for the MR2 portion to obtain a desired release profile of the drug from the MR2 portion.

45. The method of claim 44, wherein the one or more parameters is selected from the group consisting of: thickness, surface area, substrate erosion rate, and drug concentration in the MR2 portion.

46. The method of any one of claim 1-45, further comprising determining the MR1 PK curve and the MR2 PK curve and adjusting the relative amounts of the drug in the MR1 portion and the MR2 portion.

47. The method of any one of claims 1-46, further comprising determining a composite PK curve of the oral drug dosage form.

48. The method of claim 47, further comprising adjusting the relative amounts of the drug in the MR1 portion and the MR2 portion based on a comparison of the composite PK curve and the desired composite PK profile.

49. The method of any one of claims 1-48, further comprising producing the oral drug dosage form.

50. The method of claim 49, wherein the oral drug dosage form is produced by three-dimensional printing.

51. The method of claim 50, wherein the three-dimensional printing is carried out by fused deposition modeling (FDM).

52. The method of claim 50, wherein the three-dimensional printing is carried out by melt extrusion deposition (MED).

53. A method of three-dimensional printing of an oral drug dosage form designed according to any one of claims 1-52.

54. An oral drug dosage form produced by the method of claim 53.

55. An oral drug dosage form comprising a fixed amount of a drug formulated and configured to have a desired composite pharmacokinetic (PK) profile, the oral drug dosage form having two dosage units stacked back-to-back, wherein each dosage unit comprises:

an immediate-release (IR) portion comprising the drug, the IR portion having an immediate-release profile;

an extended release (ER) portion comprising the drug, the ER portion having an extended-release profile; and

a shell,

wherein the IR portion has a top surface and a bottom surface, wherein the ER portion has a top surface and a bottom surface, wherein the shell partially surrounds the IR portion and the ER portion, and wherein the shell is in direct contact with both the IR portion and the ER portion and leaves one surface of the IR portion and/or one surface of the ER portion exposed.

56. The oral drug dosage form of claim 55, wherein the drug has linear pharmacokinetics.

57. The oral drug dosage form of claim 55 or 56, wherein the shell is non-erodible.

58. The oral drug dosage form of any one of claims 55-57, wherein the IR portion and the ER portion are stacked on top of each other.

59. The oral drug dosage form of any one of claims 55-57, wherein the IR portion and the ER portion are positioned side-by-side with each other.

60. The oral drug dosage form of claim 58, wherein, at least in one of the dosage units, the IR portion is stacked on top of the ER portion, and wherein the shell leaves only the top surface of the IR portion exposed.

61. The oral drug dosage form of claim 60, wherein the bottom surface of the IR portion is in direct contact with the top surface of the ER portion.

62. The oral drug dosage form of claim 60 or 61, wherein the dosage unit further comprises a second IR portion, wherein the second IR portion has a top surface and a bottom surface, wherein the ER portion is stacked on top of the second IR portion, and wherein the shell leaves only the top surface of the IR portion exposed.

63. The oral drug dosage form of claim 62, wherein the bottom surface of the ER portion is in direct contact with the top surface of the second IR portion.

64. The oral drug dosage form of claim 58, wherein, at least in one of the dosage units, the ER portion is stacked on top of the IR portion, and wherein the shell leaves only the top surface of the ER portion exposed.

65. The oral drug dosage form of claim 64, wherein the bottom surface of the ER portion is in direct contact with the top surface of the IR portion.

66. The oral drug dosage form of claim 59, wherein, at least in one of the dosage units, the IR portion and the ER portion are positioned side-by-side with each other, and wherein the shell leaves the top surface of both the IR portion and the ER portion exposed.

67. The oral drug dosage form of any one of claims 55-66, wherein the two dosage units are the same.

68. The oral drug dosage form of any one of claims 55-66, wherein the two dosage units are different.

69. The oral drug dosage form of any one of claims 55-68, wherein substantially all of the IR portion erodes within at least about 20 minutes ~~following administration of~~ after the oral drug dosage form is to be administered to an individual.

70. The oral drug dosage form of claim 69, wherein the IR portion comprises an erodible material.

71. The oral drug dosage form of any one of claims 55-70, wherein the ER portion comprises an erodible material, and wherein the drug contained in the ER portion is released from the oral drug dosage form over a period of at least about 6 hours.