Transcript for “The Landscape of Amorphous Solid Dispersions.”

Nigel Langley: In the next minute, 250 babies will be born to add to the world's population. In the next 30 years, the world population is expected to reach 10 billion people. These are the 10 billion reasons we do what we do every day. Please join us as we explore innovative pharmaceutical solutions and sustainability and digitalization initiatives that will help us rise to the challenge.

Hi, everyone. My name is Nigel Langley. I am the host of our new BASF Pharma Solutions 10 Billion Reasons podcast series. The podcast series will consist of short discussions with our experts, highlighting different pharmaceutical technology areas or applications and industry learnings. And today, it's my great pleasure to welcome back Lindsay to the second of the podcast that she's been involved with, and also another special guest, Rajkiran. With that, before we get involved in this topic, I like, Lindsay, if you would give a few words about your introduction, and then afterwards, Rajkiran, if you could do the same, that would be fantastic.

Lindsay Johnson: Sure, thank you so much. Great to see you again, Nigel. Very happy to be welcomed back and hosted today. My name is Lindsay Johnson. I'm the Global Technical Marketing Manager for Solubilization Platform at BASF Pharma Solutions, responsible for technologies and products that are oriented towards improving solubility of poorly soluble drugs and inhibiting crystallization during, dissolution. Rajkiran?

Rajkiran Narkhede: Thanks, Lindsay. And it's been pleasure, for me to be here on this podcast series

along with Nigel. Hi, everyone. I am Dr. Rajkiran Narkhede. I am responsible for technical services in South Asia region. I am BSc in pharmaceutical sciences from University of Mumbai, and, I have over 15 years of professional experience working with various generic companies, as well as, working with BASF.

So, in my experience, I have handled on various technologies, such as, you know, extrusion modified pluralistic technologies and, specializing into the solubility area. Okay? So, with that, I'll hand it over to Nigel.

Nigel Langley: Thanks very much for those introductions. That’s really good for the listeners.

That we've got two experts here that will talk about a topic that's very important for poorly soluble drugs, and that's amorphous solid dispersions, or, ASDs as they're referred to in the industry.

So first of all, I'd like, maybe Lindsay, you could comment first on, can you describe an amorphous solid dispersion, and maybe give some reasons for why they're important in solubilization of drugs?

Lindsay Johnson: Sure, absolutely. So, amorphous solid dispersions, they're commonly used to deliver poorly soluble, small-molecule drugs. At their basic simplicity, ASDs are a blend of an amorphous drug, either at its molecular level or within small, amorphous regions that are kinetically trapped within a polymeric matrix. And the premise of solubility enhancement from ASDs is that, upon administration, oral administration, your polymer matrix will dissolve, and it will release amorphous drug, which has a higher solubility than the crystalline form of the drug. So, you're delivering a higher, solubility form of the drug, and in that case, improving solubility and bioavailability.

Nigel Langley: Sure. Now, Rajkiran, do you have anything else to add to that? That is a very good description of ASDs.

Rajkiran Narkhede: Yes

Nigel Langley: Thanks, Lindsay.

Rajkiran Narkhede: Thanks Lindsay and Nigel. I'm in, just to add to what Lindsay has said, amorphous solid dispersion has really become synonymous to solubility enhancement when it comes to pharmaceutical, you know, development. So, typically, there are two phenomenona, which are the with this amorphous solid dispersion, and we call it as, "The spring and the parachute," effects.

The spring is kind of an effect which we get using amorphous solid dispersion that, in a way is a quick solubility enhancement and where we get a very quick initial concentration of the drug. Followed by that, it actually gives us some parachute, which helps that the drug concentration is there into the blood for a prolonged period of time. So, what it does help is that, you know, it maintains the thermodynamics of the systems, and, you know, it inhibits precipitation of the drug, which is actually dissolved into this solid matrix. So, with that, I think I, would like to hand it over to you again, Nigel.

Nigel Langley: Okay. So, we're talking about polymers that have a solubilization effect and maybe, avoid this recrystallization that does occur from amorphous solid dispersions. Does that, is that what I'm understanding? And, so, it's a challenge, and I'm aware myself that there's a solubility challenge still in drug development. And at today, that's very serious and very important. So, maybe, Lindsay, you can sort of describe, if you may, what the market landscape for solid, amorphous solid dispersions are?

Lindsay Johnson: Sure, Nigel. And just like you said it's very important. The topic of poor solubility is a growing concern, and it's one that we're familiar has a, big burden on the

future-development pipeline of, NCEs coming to market. So, I would say that the landscape of commercially available ASDs has really changed dramatically over the last 15 years, pretty much from 2007, which was when KALETRA was approved and brought to market, onward.

And so, since 2007, there's now over probably 30 marketed drug products that are made as amorphous solid dispersions approved by the FDA. We're very familiar, with products from Vertex, from Gilead, from AbbVie, and others. And, you know, these are split between different methods of production. So, amorphous solid dispersions, they can be made in multiple ways, and we're seeing APIs being brought to market through a variety of, manufacturing techniques, including hot melt extrusion, for example, and spray drying and a few other techniques like solvent evaporation as well.

Nigel Langley: Interesting. So, maybe Rajkiran you can sort of highlight, if you may, HME, or hot melt extrusion, as a process. And why is that often preferred over spray drying or as an alternative to spray drying? Maybe you can share your insight into that.

Rajkiran Narkhede: Yes, Nigel definitely. So, amongst the technology that Lindsay described, hot melt extrusion is a predominant one, when it comes to formulation of amorphous solid dispersions. And this is a technology which is really, you know, easy to scale up as well. What, customer need to do is that they need to have, a special set of equipment, only one, that is hot melt extruded. And once they have it installed into their, you know, their facility, then the, all the down-streaming process actually becomes very simple.

So, this HME is used for APIs that are thermally stable. And typically, those not soluble in organic solvents. So, HME really plays a role over there. And this thermal sensitivity appears, however, maybe more suitable for spray drying. But in majority of the cases, HME do work and, solubility is, actually in an appropriate spray solvent, is a prerequisite of course for the spray drying.

And however, both the technologies are effective for improving the bioavailability of poorly soluble drugs, the HME still remains a choice, a technology of choice, considering it's easy, handling, as well as easier down-streaming. Yeah. So, yeah. This is how it is onto the selection of hot melt extrusion or spray drying.

Nigel Langley: Okay. But it's an alternative, isn't it? It's just an option for a formulator, to have. And my, insight there would be, some companies prefer to use one technique over another. Is that what you're seeing as well

Rajkiran Narkhede: Yes

Nigel Langley: … you have that option?

Rajkiran Narkhede: Yes, yes. They have option. And definitely based on the merit of the API, you know, definitely the selection goes, but then the more preferred on, amorphous solid dispersion will be hot melt extrusion.

Nigel Langley: Can you touch on the continuous manufacturing opportunity for HME as well? is that another advantage that you, see?

Rajkiran Narkhede: Yes, definitely Nigel, a very good point. And, continuous manufacturing is, something which is very much possible using hot melt extrusion simply because of the setup, you know? We have an extruder, and the product coming out from the extruder can be continuously fed for the next operations, such as milling as well as blending, and taken to the compression.

So, in a way, a very likely compression. You know what we can say, a continuous manufacturing setup can be established using hot melt extrusion. So, this is really possible with this.

Nigel Langley: Thank you, Raj, again. That's, that's very insightful.

Rajkiran Narkhede: Yeah

Nigel Langley: And so, on our last podcast that Lindsay actually appeared or presented at, we talked about soft gels. And part of that was, SEDDS and SMEDDS, you know, self-emulsifying drug delivery systems. And that was something also as an alternative or an option for, poorly soluble drugs as well. Is there... I am intrigued, Lindsay, if you could make some comment on, you know, why ASDs, compared to lipid-based systems, what is the choice that formulators have, and why do they make that choice?

Lindsay Johnson: Sure. And you know, I can definitely put, a list of pros on each side. And so, I think it's very much as Rajkiran mentioned, the API is a lot of times going to dictate your choice. If you have a low-melting point, greasy API, this may not be amenable and comprise your solid-state stability in that way. Whereas if you have a brick dust, or a very high melting point API, this is something that is more likely to be stable as an ASD, and in that case can kind of expand into that direction.

One of the key advantages that we see for ASDs is the ability to provide the final drug product as a tablet, which still remains the most common oral-dosage form. And just as Rajkiran altered, alluded to earlier, nearly all pharmaceutical companies have the tableting equipment, so as you form the ASD, you can merge into the downstream processing of the conventional tablet, equipment. So, that way ASDs are more accessible, I think, in, in some scenarios to a wider range of, pharmaceutical companies.

We do also see that drug load is higher for ASDs; so, whereas lipid-based-drug-delivery systems conventionally have a maxim drug load per capsule of about 100 milligrams, you can load higher, up to let's say maybe 30 to 40% of a

tablet, so maybe 300 to 400 milligrams of your API. So, a little bit of it depends on the API nature itself, but then also the dose level that you're needing to achieve, what technique, what solubilization technique you might go for in that case.

Nigel Langley: Thank you very much for that very detailed explanation. And I'm just also intrigued if, there's a future innovation part to the ASDs, Rajkiran. Maybe you could comment on where is the direction going in this area? what are the developments in innovations around ASDs that you see may come in the future?

Rajkiran Narkhede: Yes, Nigel, a very good question. So on, the academic advances, I think there are several universities piloting onto the various technologies related to amorphous solids dispersions. Some of them, very innovative ways what we have seen very recently is that, along with using a polymeric matrix, the academia are also trying to combine the benefits of lipids along with this polymeric matrix, and wherein they see enhanced solubility as well as measuring the kind of a supersaturation for a prolonged period of time.

Along with that, there are some more different ways of manufacturing, these particular ASDs, such as drug layering, simplest one, but still effective. And, very innovative technologies coming up, such as KinetiSol. And again, in contradict to, and contradictory to some of the complex technology, some simpler ones like directly absorbing this dissolved re-polymer, you know, solution, onto the granular carrier, such as Mannitol.

This, also develop some of the advances which are coming up with the formulation scientists, you know, approaching into this particular, area of amorphous solid dispersions. Also there are some instances wherein the APIs are pretreated using, the polymeric matrices maybe during the last stage of crystallization. And when the final product comes out, we see that it is in the form of crystalline, or, it is in the form of amorphous solid dispersion. So, these are some of the advances that are coming up, through academia and also to industry in this area.

Nigel Langley: And can you explain briefly the manufacturing processes for amorphous solid dispersions or ASDs?

Rajkiran Narkhede: Oh, of course, HME is used for APIs, that are thermally stable or are not suitable in organic solvents. Thermally sensitive APIs may be more suitable in spray drying. Solubility in an appropriate spray solvent is a prerequisite, of course, for spray drying.

Okay. So, what technologies are effective for improving the bioavailability of poorly soluble drugs? Of course, the properties of the API and the capabilities of the developing labs, it will really steer the selection of the technology.

Nigel Langley: Thank you, Rajkiran. That is very interesting as well because, obviously this process is going to be here for the future. And, would you say that, there's interest both in the generic side as well as the new-chemical entities side, the innovative side?

Rajkiran Narkhede: Yes.

Nigel Langley: … just as a last part of this podcast, maybe Lindsay, you could shed some light on that for me.

Lindsay Johnson: Sure, I think Rajkiran is the expert in the generic and CDMO space. So, maybe Rajkiran will give it to you to start, and then, I will close us out.

Rajkiran Narkhede: Yes, definitely. So, Nigel has rightly asked me that, whether only it is with the innovator, with generics. I would say with, if it is with the innovator, it is likely to come with generics also. And moreover, for the valuated generics, there is more and more scope wherein customers are trying to develop some appreciated approaches, wherein the solubility was achieved using a conventional way. People are coming up with supply-form technologies, using some innovative ways to formulate amorphous solid dispersions. And, with that, they are able to achieve this value added generics.

And, with, with respect to, this rule of CDMOs in this amorphous solid dispersions, I would say a lot of partnership is ongoing, with the CDMOs. And this is for the reason that CDMOs do carry some of the expertise, with respect of a formulation capabilities and to this expertise. They have a good collaboration with academia as well as with some of the contract manufacturers. And all this synergy helps them to deliver a good amorphous solid dispersion kind of for technologies to the customers. So, definitely there is an important role of CDMOs in creating some innovative space in, formulating amorphous solid dispersions.

Lindsay Johnson: Yeah. I think the future, Nigel, as you were asking on for ASDs, it- it's in, two phases, right? We have these generics that are coming to market because 2007 was about 15 years ago, and you're having this off-patent products that are now coming forward. We do see some, just as Rajkiran alluded to, value add in some of the generics. We've seen the matrix, for example, change from the NDA to the AND in a couple of cases, based on hot melt extrusion or spray drying.

And, you know, we're certainly going to see new approaches to ASDs and maybe new chemistries and formulations coming as part of that, growth in both the NCE space as well as the mentioned generic space for it. So, really excited to see where it goes. Obviously, 90% of the pipeline is BCE Class II and IV, as we well

know, so there will be more and more of these products coming to market over the coming years.

Nigel Langley: Thank you very much. That ends our podcast today. And I'd just like to thank again Lindsay and Rajkiran' s expertise in this area and their sharing some of their thoughts, around solubilization with poorly soluble drugs. And with that, stay tuned. There will be a, a future podcast coming around the corner. Thank you very much. Thank you.

Speaker 4: BASF, we create chemistry