Case study – Application of Colorista® capsules for rapid product development with proof of concept data for a heat, oxygen, and moisture sensitive compound.

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PURPOSE

To design a suitable solid oral delivery system with an acceptable shelf life at room temperature or at refrigerated conditions for bomedemstat (IMG-7289). IMG-7289 is:

- Easily oxidized
- Susceptible to hydrolysis

METHODS

The study progressed as follows:

Excipient compatibility

- Binary mixtures API : Excipients
  - Fillers, binders, stabilizers, lubricants, glidants, disintegrants, and coating materials
- Evaluated for 2 weeks at accelerated condition 1 and accelerated condition 2 for degradation products

Blend study

- To optimize the concentration of stabilizer needed to prevent degradation of IMG-7289 in a blend
- Formulations A-D were designed with various ratio of IMG-7289 : stabilizer
- Evaluated for 2 weeks at accelerated condition 1 and accelerated condition 2 for degradation products

Selection of manufacturing process

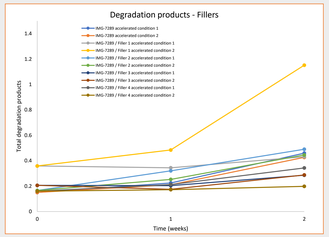
- To evaluate direct blend vs wet granulation process
- To evaluate tablet dosage form vs capsule dosage form
- Compression was performed using high speed rotary tablet press while encapsulation was performed manually
- Evaluated for 5 weeks at accelerated condition 1 and accelerated condition 2 for degradation products

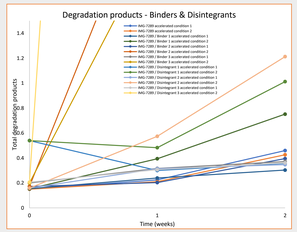
Scale-up

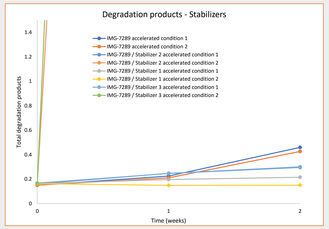
- The manufacturing process batch was scaled-up 6X for each dose
- Encapsulation performed using automatic encapsulator
- Encapsulation performed in white opaque as well as Colorista® capsules
- Finished product evaluated for Uniformity of Dosage Units and Dissolution
- Evaluated for 16 weeks at controlled room temperature (CRT) and accelerated condition 1 to monitor the trend in degradation products

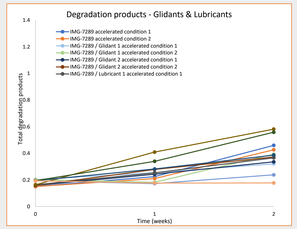
RESULTS

Excipient Compatibility Study results



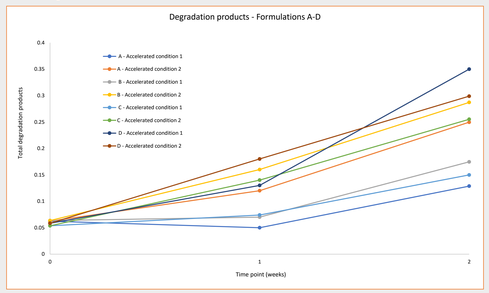






- 3 fillers, 1 disintegrant, 1 binder, 1 glidant, 3 lubricants, and a stabilizer identified as the excipients of choice for formulation development with IMG-7289.
- The degradation products observed in the 2 weeks excipient compatibility study were observed to be lower in the presence of the selected stabilizer than the total impurities observed in a control sample without the stabilizer.

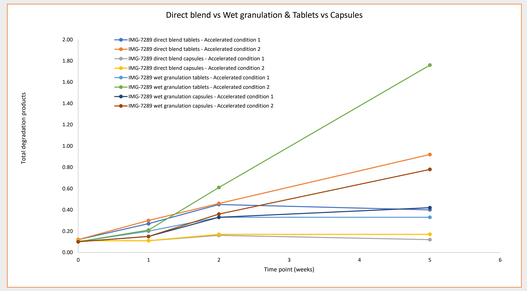
Blend study



- The selected stabilizer was evaluated at three different concentrations (increasing order) in formulations A, B, C, but the results do not present a difference in stability profile for any concentration evaluated.
- Formulation D was designed as control with no stabilizer

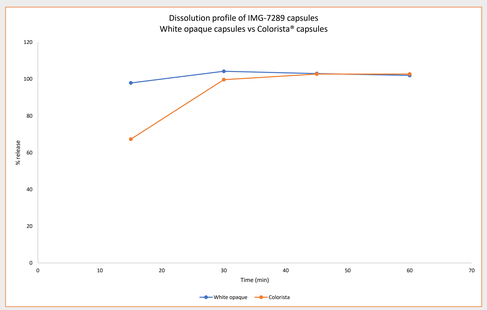
Manufacturing selection process

- The blends were manufactured using a direct blend manufacturing process in a V-shell blender, or via a high shear granulation and fluid bed drying process prior to compression or encapsulation.
- Compression was performed on a high speed rotary press using a single punch, whereas encapsulation was done manually in size 0 white HPMC capsules.
- Capsules manufactured via the direct blend process proved to be the most stable formulation when evaluated for a period of 5 weeks at accelerated stability conditions, thereby eliminating tablet dosage form and wet granulation process



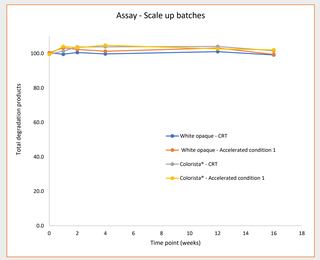
Scale-up batch - processability

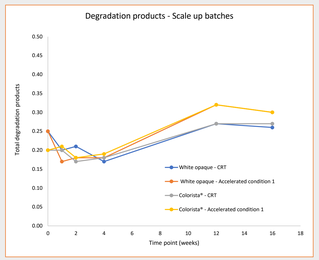
- The process was scaled up to enable processing on high-speed automatic encapsulator using white opaque & Colorista® capsules
- Passing content uniformity (CU) results indicated successful scale up of lab-scale batches using automated encapsulator
- Scale-up batches evaluated for dissolution indicated acceptable results with (Q 80 %) achieved in 30 minutes.



Scale-up (continued)

- Following were the observations when scale-up formulations were evaluated for 16 week at CRT and accelerated condition 1:
  - Assay and degradation products results were acceptable for white opaque and Colorista® capsules up to 16 weeks at both conditions
  - Assay and degradation products results were comparable for white opaque vs Colorista® capsules indicating no significant impact of capsule color on the stability of the formulated finished product





CONCLUSIONS

- Stabilizer played a significant role in controlling the total impurities in the formulations containing IMG-7289.
- Capsule dosage manufactured using a direct blend manufacturing process exhibit better stability than tablet dosage form using IMG-7289.
- The lab scale blends when scaled up were successfully encapsulated using the automated encapsulator with passing content uniformity results. Thus the manufacturing process is scalable to clinical scale equipment. This was proven for white opaque as well as Colorista® capsules
- Colorista® capsules exhibited comparable Assay, degradation products, and dissolution results when compared to white opaque capsules indicating the successful use of Colorista® capsules in the initial stages of product development.

Colorista® Capsules

ACKNOWLEDGEMENTS

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