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Historical Evolution and Provider Awareness of Inactive Ingredients in Oral Medications

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Historical evolution and provider awareness of inactive ingredients in oral medications

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ABSTRACT (200 words)

Purpose A multitude of different versions of the same medication with different inactive ingredients are currently available. It has not been quantified how this has evolved historically. Furthermore, it is unknown whether healthcare professionals consider the inactive ingredient portion when prescribing medications to patients.

Methods We used data mining to track the number of available formulations for the same medication over time and correlate the number of available versions in 2019 to the number of manufacturers, the years since first approval, and the number of prescriptions. A focused survey among healthcare professionals was conducted to query their consideration of the inactive ingredient portion of a medication during prescriptions.

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Results The number of available versions of a single medication have dramatically increased in the last 40 years. The number of available, different versions of medications are largely determined by the number of manufacturers producing this medication. Healthcare provides commonly do not consider these the inactive ingredient portion when prescribing a medication.

Conclusions A multitude of available versions of the same medications provides a potentially under-recognized opportunity to prescribe the most suitable formulation to a patient as a step towards personalized medicine and mitigating potential adverse events from inactive ingredients.

ABBREVIATIONS

API Active Pharmaceutical Ingredient

FDA Food and Drug Administration

IRB Institutional Review Board

NDC National Drug Code

NIH National Institute of Health

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INTRODUCTION

Inactive ingredients, also known as excipients, are defined by the FDA as those that are not the active compounds in a given formulation [1], but it is a distinction that can be dependent on the dose. For instance, simethicone and polyethylene glycol are two examples of chemicals that are commonly utilized as inactive ingredients but are also the key active ingredient in widely-used over-the-counter medications. [2] When added in low quantities to oral solid dosage forms, inactive substances in a formulation are not intended to have a direct therapeutic effect, but they can have important chemical properties that facilitate absorption or product characteristics such as taste, color, or shelf-life. [3] The amount of a given inactive ingredient in an approved product can serve as a precedent and help to facilitate the development of new products that use that excipient below established levels. [1]

Patients can experience adverse events triggered by a wide range of substances designated as inactive ingredients. For example, a small number of patients are allergic to inactive ingredients, typically food derivatives, dyes, or preservatives. [4–7] Patients with celiac disease or gluten sensitivity may be irritated by gluten-containing inactive ingredients. [8,9] Artificial or fermentable sugars can further cause gastrointestinal distress in intolerant patients or those with irritable bowel disease. [10] A majority of medications may contain such ingredients, and it is common for different products containing the same active pharmaceutical ingredient (API) to contain different inactive ingredients. [4] However, there has been scant published work seeking to quantify the change in the use of inactive ingredients over time and whether healthcare providers are considering the multiplicity of inactive ingredients when prescribing a medication. Here, we sought to evaluate the historical evolution of different formulations available in US medications. Furthermore, we sought to query physicians about their awareness of inactive ingredients and whether they consider the excipients when evaluating a patient who reports an adverse reaction to an oral medication.

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MATERIALS AND METHODS

Historic data analysis

We extracted the listed active ingredients, inactive ingredients and NDC codes for all oral solid dosage forms marketed in the United States from the National Institute of Health's Pillbox (version 201605). [11] The names of active and inactive ingredients were then subsequently processed as previously described. [4] Briefly, we standardized names of ingredients to lowercase, corrected spelling errors, and standardized formatting. A "formulation" was defined as a unique combination of specific inactive ingredients and active ingredients, in which the active and inactive ingredients could occur in any order in their respective list. This does not account for differences in quantities since this information is not currently available. Using the NDC codes from Pillbox data as a reference, we extracted from DrugBank 5.0 [12] the identity of the manufacturer, the marketing data, and the date the product was discontinued, if applicable. This generated a list of all marketed oral solid dosage forms with their active and inactive ingredients, their marketing period, and their manufacturer. We further processed this data in KNIME [13] as well as in Python using pandas to group different marketed dosage forms of the same API, thereby enabling us to track the number of available formulations and the number of manufacturers over time. For each API, we correlated the number of currently available formulations (number of solid dosage forms with active marketing in 2019) with the years since products containing the specific API were first approved (2019 - first marketing year for this API), the number of manufacturers (producing this API in 2019), and the number of prescriptions in 2019. The latter was extracted from the MEPS top 300 prescribed medicines file from the ClinCalc DrugStats Database (clincalc.com) and manually linked to our data through the name of the API.

Survey

Study data was collected and managed using REDCap electronic data capture tools (version 7.4.19) hosted at Partners Healthcare [14]. A PDF of the complete survey instrument is included as a supplement (Electronic Supplementary Material). Data that could identify study participants was not collected, and the survey was determined to be exempt by the Partners Healthcare IRB. Surveys were distributed via internal listservs with electronic reminders to the internal medicine house staff at the Brigham and Women's Hospital (219 recipients), endocrinology fellows and faculty within Partners Healthcare (85 recipients), and gastroenterology fellows and faculty within Partners Healthcare (94 recipients). Determination of a chemical's status as an active ingredient, inactive ingredient, or both was based on queries of the NIH pillbox data [11] and the FDA's Inactive Ingredient Database [15]. The word "magnesium" was used on the survey and was intended to mean magnesium oxide, which is used both as an API and an inactive ingredient. "Cellulose" is an inactive ingredient, although the chemically related "methylcellulose" is used as an active ingredient. To capture such differences, we here exclusively focused on the "inactive ingredient" classification. Similarly, although "gluten" can be present in pharmaceutical products through contamination, it is itself not used purposefully as either active or inactive pharmaceutical compound and was therefore here considered "neither". One ingredient that was included in the surveys but not included in the analysis was mercury. We decided that mercury was potentially confusing to participants: it is not an API or an inactive ingredient in FDA-approved medications, but it is an API in homeopathic drugs in the Pillbox database (e.g. NDC Codes 54973-3134-1 and 48951-7043-4) and, in compounds like thimerosal, can be found as a component of inactive ingredients in injectable formulations. [16]

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Statistical analysis and plotting

Data was analyzed in Python (version 2.7.6) using the Numpy (www.numpy.org) and SciPy (www.scipy.org) libraries. Survey data was visualized using SankeyMatic (www.sankeymatic.com). Other plots were generated using matplotlib (www.matplotlib.org). All plots were processed in Inkscape (version 0.91). Statistical tests and statistical analysis were performed in Python (version 2.7.6) and Prism (version 7.03). Specifically, for analyzing the correlations between the number of available formulations in 2019 and the number of manufacturers in 2019, years in production, and number of prescriptions in 2019, we determined the Pearson correlation coefficient and calculated a two-sided *p* value using a beta distribution as implemented in scipy.stats.pearsonr. For the analysis of correlations between the survey responses, we calculated Fisher's exact test using the unconditional Maximum Likelihood Estimate as implemented in scip.stats.fisher_exact. Results were not corrected for multiple testing since even without this correction all differences in responses were insignificant. To analyze differences in the error rates of different classes of ingredients for the quiz, we imported the data into Prism and performed an ordinary one-way ANOVA without matching. Error rates were further contextualized by comparing mean values and one standard deviation.

RESULTS

The number of available formulations has increased exponentially

By combining medication formulation data with marketing data, we were able to investigate how the number of available formulations per API has changed over time. We found that the number of formulations per API varied depending on the active ingredient investigated (Figure 1A), but we generally observed an overall increase in the number of available formulations in the last forty years (Figure 1B). The medications acetaminophen (286), ibuprofen (245), diphenhydramine hydrochloride (226), and aspirin (212) had more than 200 available formulations in the year 2019, excluding combination products. On average, there were 8.75 alternative formulations available per medication in 2019. Notably, the number of available formulations seems to be most strongly correlated (Figure 1C) to the number of manufacturers producing the product (r=0.84, p = 3e-63) rather than the number of years a medication has been on the market (r=0.21, p = 2e-3) or the number of annual prescriptions of the medication (r=0.38, p = 1e-9).

Survey among healthcare professionals reveals limited awareness

88 completed surveys were received (22% response rate). Residents in internal medicine (n=49, 55.7%) slightly outnumbered attending physicians (n=30, 34.1%), with the most common specialty being gastroenterology (63.9% of specialists, n=23) (Table 1). In addressing baseline attitudes towards generic medications, the survey first presented a scenario where a patient with celiac disease and an intolerance to lactose is started on generic metformin and develops diarrhea without any additional allergic symptoms (Table 2). Most professionals would only select a single intervention (71 respondents, 81%), while some others (16, 18%) selected two strategies, and one participant selected three strategies (Figure 2A, Table 2). The majority of providers (n= 49, 55.7%) indicated that they would offer reassurance, while others would document an intolerance (n=20, 22.7%) or switch classes (n=20, 22.7%) (Figure 2A, Table 2). A smaller

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number would switch to a branded version of the drug (n=9, 10.2%) or switch to a different generic manufacturer (n=10, 11.4%).

Almost all (n=79, 89.8%) of the providers had encountered a patient who insisted that there was a difference between the generic and branded form of a medication at some point in their career (n=79), and approximately 94% (n=74) of these providers had encountered at least one patient who made this assertion in the past year (Figure 2C, Table 2). Approximately half of these providers (n=41, 51.9%) believe that there is a difference between generic products (Table 3), but when asked about the components of generic and branded drugs, 100% (n=88) correctly recognized that they both had the same active ingredients and 95.4% (n=84) recognized that they have different inactive ingredients (Table 4). Less than half of providers know where to find the inactive ingredients in their patients' medications (n=36, 40.9%), and while 75% (n=27) of that subset have looked up these ingredients, only 25% (n=9) do it more than once a month (Figure 2C).

When asked to identify whether chemicals are active ingredients, inactive ingredients, neither, or both, more than 66% of participants were able to successfully identify compounds as either active or inactive in all circumstances (Figure 2B, Table 4). However, less than 30% correctly identified any of the three compounds that can be designated as both active and inactive ingredient, depending on the concentration. Error rates differed significantly between the different ingredient classes (one-way ANOVA, $p = 0.006$) and were lowest for active ingredients (3.4%), higher for inactive ingredients (22% ± 8%) and highest for ingredients that can serve both as active or inactive ingredients (80% ± 10%).

DISCUSSION

Generic drugs comprise ~90% of prescriptions in the United States [17] and save hundreds of billions of dollars annually, [18] but the formulation differences between different medications is potentially a misunderstood and underappreciated factor in healthcare providers and patients. For some commonly prescribed medications, there are hundreds of different versions of the same medication available to patients today. Our data suggests that this is mostly driven by different manufacturers, where each manufacturer produces a different formulation for the same medication. However, this is likely still an underestimate of the true variability. For example, manufacturers are required to list the inactive ingredients included in a formulation but not the amounts at which these ingredients are included – which can vary greatly between products [19].

Patient hypersensitivity or intolerance to a new medication can be challenging for both patients and health care providers, but the range of available formulations could represent an underrecognized clinical opportunity. When a patient experiences medication side effects, it is sometimes difficult to attribute those symptoms to the API or an inactive ingredient. Incorrectly parsing the difference could mean switching to costlier or less effective medications rather than switching generic manufacturers. Our survey focused on intolerance and allergy symptoms, but there is increasing evidence that certain inactive ingredients may influence the pharmacokinetic or pharmacodynamic profiles in patients, [20-22] and such different formulations might result in different exposure profiles to the APIs. Unfortunately, our survey findings show that healthcare providers are often either unaware of these alternatives or lack the information needed to navigate this important part of the available prescriptions. Our survey is fairly focused in scope and included a large fraction of newly training practitioners, which is a notable limitation but also serves to suggest that there may be potential opportunities in the education of healthcare professionals.

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CONCLUSIONS

Together, this data shows that formulation heterogeneity is an increasing and potentially under-recognized source of medication-related adverse events, patient discomfort, and non-compliance. Considering both the active and inactive ingredients may be helpful when prescribing medications and understanding side effects, and this could be worth emphasizing to prescribing clinicians. Innovative novel formulations as well as expanding clinical decision making to consider currently available formulations will both provide currently unrecognized opportunities to control adverse effects as well as impacting adherence to and the pharmacokinetics of life-saving medications.

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COMPETING INTERESTS

Complete details of all relationships for profit and not for profit for G.T. can be found at the following link: www.dropbox.com/sh/szi7vnr4a2ajb56/AABs5N5i0q9AfT1IqIJAE-T5a?dl=0. S.M.B. has a consulting relationship with Two River Consulting and is an equity holder in Kronos Bio Inc. D.R. acts as a mentor for the German Accelerator Life Sciences. D.R., S.B., and G.T. are co-inventors on a provisional patent application 62/811, 502 encompassing systems and algorithms capable of quantifying and providing inactive ingredient burden in medications.

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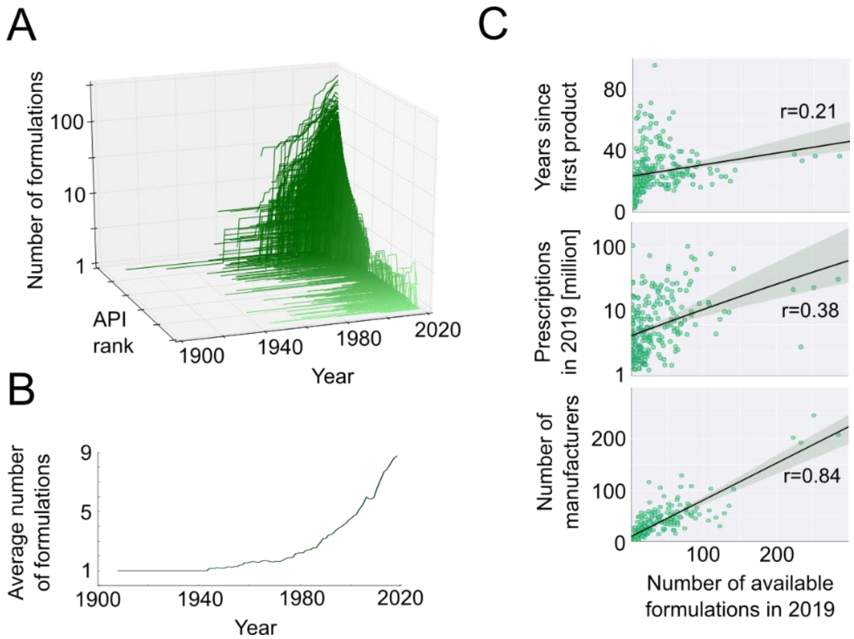

Figure 1: Historic evolution of the number of available formulations. **A** Combined DrugBank and Pillbox data track the number of different formulations of the same APIs available to patients over time, ranked by number of formulations available in 2019. **B** Average number of available formulations per API. **C** Correlations of the number of formulations available for the 300 most prescribed medications of 2019.

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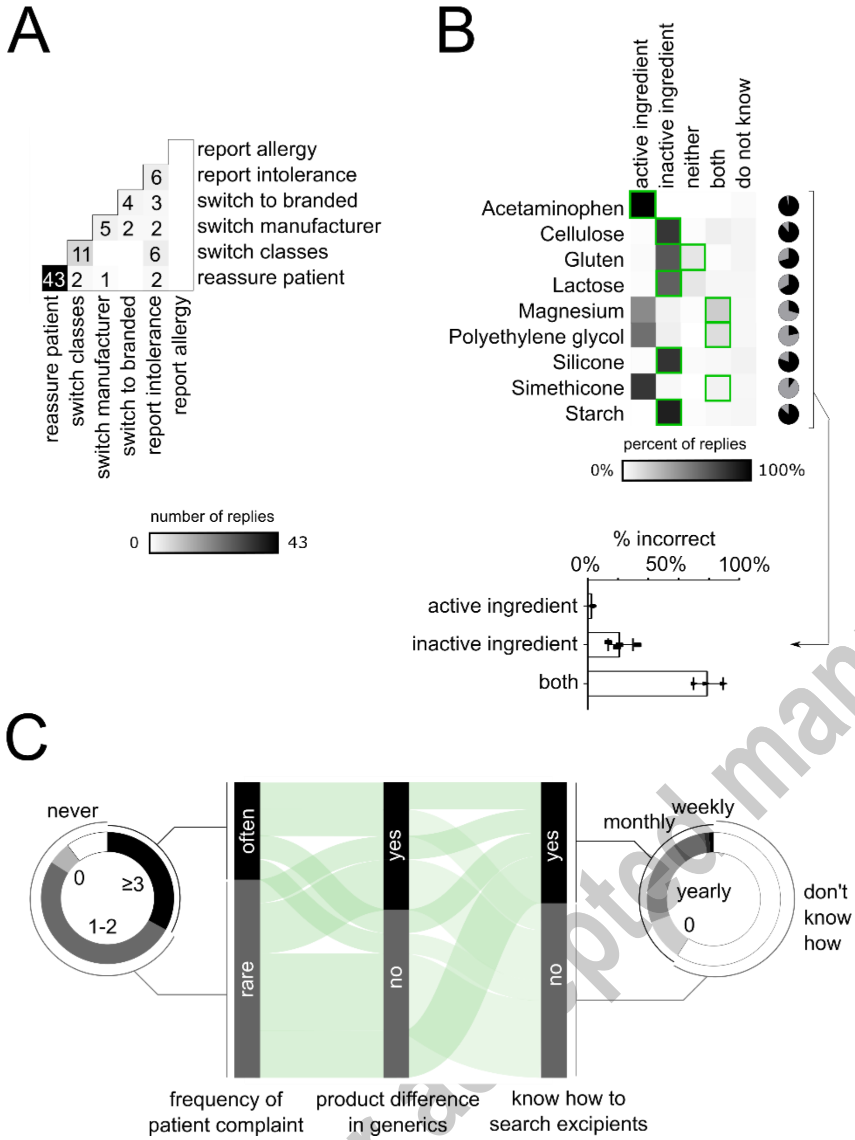

Figure 2: Summary of survey data among healthcare professionals (Electronic Supplementary Material). **A** 2D heatmap showing the replies to a case study of a patient with type II diabetes, well-controlled celiac disease, and lactose intolerance who developed gastrointestinal symptoms after starting metformin. **B** Analysis of quiz results asking participants to designate chemicals as "active ingredient", "inactive ingredient", "both" inactive and active ingredient, or "neither". The correct answer is highlighted in green, and a 2D heatmap showing number of replies. **C** Survey results regarding patient concerns about generic drugs and provider searches for excipient information. The pie chart on the left shows the percentage of survey participants whose patients insisted that a generic medication affected them differently on an annual basis: "never" and previously but not in the last year ("0") are denoted separately.

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Table 1 - Demographics of Survey Respondents.

Gender (n=88)	**No. (%)**
Male	42 (47.7%)
Female	46 (52.3%)
I prefer not to answer	0 (0%)
Role as a provider (n=88)	
Medical resident	49 (55.7%)
Attending specialist provider	30 (34.1%)
Fellow	6 (6.8%)
Other	2 (2.3%)
Nurse practitioner	1 (1.1%)
Subspecialty* practice *or training (n=36)	
Gastroenterology	23 (63.9%)
Endocrinology	12 (33.3%)
Cardiology	1 (2.8%)
Years since completing training (n=88)	
Still in training	55 (62.5%)
<5 years	12 (13.6%)
5-10 years	6 (6.8%)
11-20 years	5 (5.7%)
21-30 years	5 (5.7%)
>30 years	5 (5.7%)
Practice Setting (n=88)	
Inpatient	5 (5.7%)
Outpatient	10 (11.4%)

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Both inpatient and outpatient	72 (81.8%)
Neither	1 (1.1%)
Percentage of time devoted to clinical activities (n=30)	
No clinical time	1 (3.3%)
<25% clinical time	8 (26.7%)
26-50% clinical time	4 (13.3%)
>50% clinical time	17 (56.7%)

Table 2: Provider reactions to medication-attributed symptoms.

A patient with well-controlled celiac disease and lactose intolerance was started on generic metformin and now presents with mild abdominal pain, bloating, and diarrhea. Which of the following would you do next? Please select all that would apply (n=88)	
Document a medication allergy	0 (0%)
Document a medication intolerance	20 (22.7%)
Switch to branded metformin	9 (10.2%)
Switch to another manufacturer	10 (11.4%)
Switch classes	20 (22.7%)
Provide reassurance only	49 (55.7%)
Have you ever experienced a patient who insists that the generic form of a medication or tablet affects them differently than the branded version of the same medication?	
No	9 (10.2%)
Yes	79 (89.8%)
If yes, how often has this happened in the past year? (n=79)	
None	5 (6.3%)
One to two times	45 (57%)
Three or more times	29 (36.7%)
If yes, is there a difference in the products or is this patient preference? (n=79)	
Difference	38 (48.1%)

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Patient preference	41 (51.9%)

Table 3: Generic Skepticism Index [23] **and Knowledge of Active and Inactive Ingredients.** Participants responses on a five-point scale of drug skepticism and true/false questions on the definition of active and inactive ingredients.

	Strongly disagree	**Somewhat disagree**	**Neither agree nor disagree**	**Somewhat agree**	**Strongly agree**	**Skeptics [23]**
Have similar efficacy	1 (1.1%)	2 (2.3%)	3 (3.4%)	34 (38.6%)	48 (54.5%)	6 (6.8%)
Have similar safety profiles	0 (0%)	2 (2.3%)	0 (0%)	24 (27.3%)	62 (70.5%)	2 (2.3%)
Cause more adverse events	46 (52.3%)	31 (35.2%)	8 (9.1%)	3 (3.4%)	0 (0%)	11 (12.5%)

	True	**False**
Have the same active ingredients	88 (100%)	0 (0%)
Have the same inactive ingredients	4 (4.5%)	84 (95.5%)

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Table 4: **Classification of chemicals as active or inactive ingredients.** Correct answers are indicated by bold font. If participants designated that they were "Unsure" or selected the incorrect answer, it was considered that they "Did not know" the correct answer. Responses for "mercury" were suppressed from the summary figure because the classification was potentially confusing.

	Active ingredient	**Inactive ingredient**	**Neither**	**Both**	**Unsure**	**Did not know**	**95% CI**
Acetaminophen	**85 (96.6%)**	0 (0%)	0 (0%)	0 (0%)	3 (3.4%)	3%	[1.17 - 9.5%]
Cellulose	1 (1.1%)	**70 (79.5%)**	1 (1.1%)	10 (11.4%)	7 (6.8%)	89%	[80.3 - 93.7%]
Gluten	3 (3.4%)	62 (70.5%)	**15 (17%)**	1 (1.1%)	7 (8%)	30%	[21.0 - 39.8%]

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Lactose	2 (2.3%)	**59 (67%)**	15 (17%)	6 (6.8%)	6 (6.8%)	33%	[24.0 - 43.3%]
Magnesium	46 (52.3%)	9 (10.2%)	2 (2.3%)	**26 (29.5%)**	5 (5.7%)	71%	[60.2 - 79.0%]
Mercury	5 (5.7%)	42 (47.7%)	20 (22.7%)	**7 (8%)**	14 (15.9%)	92%	[84.5 - 96.1%]
Polyethylene glycol	54 (61.4%)	10 (11.4%)	0 (0%)	**19 (21.6%)**	5 (5.7%)	79%	[68.7 - 85.7%]
Silicone	1 (1.1%)	**71 (80.7%)**	3 (3.4%)	4 (4.5%)	9 (10.2%)	19%	[12.4 - 28.8%]
Simethicone	70 (79.5%)	4 (4.5%)	0 (0%)	**9 (10.2%)**	5 (5.7%)	90%	[81.7 - 94.5%]
Starch	0 (0%)	**76 (86.4%)**	2 (2.3%)	4 (4.5%)	6 (6.8%)	14%	[7.8 - 22.3%]

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