

Design, Optimization, and Evaluation of Combined Dosage form of Amoxicillin and Nonsteroidal Anti-inflammatory Agent for Pediatric use using DoE

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Abstract

Introduction: Combination therapy is gaining high attention in pharmaceutical industry. It provides many advantages in accuracy of dose and patient compliance, especially in pediatrics. This work aims to formulate successful fixed-dose combination pediatric oral dosage form as orodispersible tablets (ODTs) which contain a combination of amoxicillin 125 mg as an antibiotic and ibuprofen 100 mg per tablet for the treatment of several pediatric illnesses that need this combination. **Materials and Methods:** Design of experiment (DoE) was used to design the best formula for the proposed combination. The selection of non-active materials based on the improvement of tablet characteristics, taste, and safety. Then, DoE was used to predict the best combination of additives that give the best criteria of ODTs. The three responsive factors were wetting time and disintegration time and dissolution of both drugs taken as 70% of drug is dissolved at or in <30 min. Moreover, the three materials which were found to affect these responsive factors are sodium starch glycolate, Avicel, and sucrose. The optimized formula then was prepared and evaluated. **Results and Discussion:** Results were treated and the best combination of the affecting materials was confirmed by DoE that fitted the criteria of ODT. The optimized formula gave results which were very close to the predicted results by the DoE regarding the three response factors. **Conclusion:** Successful design was achieved using DoE, economic, and easy in production and achieved the goals of the design.

Key words: Amoxicillin, DOE, fixed combination therapy, ibuprofen, orodispersible tablets, pediatric preparation

INTRODUCTION

Fixed combination therapy (FCT) is dosage forms that contain >1 active pharmaceutical ingredient (API) combined in a single dosage form.^[1] These combinations aim either to achieve multiple therapeutic paradigms or synergism.^[2-5] Combination therapy has an advantage of patient's compliance by decreasing the "pill burden" for them.^[6] Since combination therapies are reviewed by the Food and Drug Administration in the US, the active ingredients used in the FCT are unlikely to show adverse effect with each other.^[7] FCT adds another advantage to drug companies by expanding their marketability and providing different variability in drug products.^[8] However, FCT faces challenges in compatibility and stability of APIs which are combined.^[9] In pediatrics, patient compliance has an additional advantage in health care of young patients.

Oral drug delivery remains the most widely accepted and convenient dosage form among population. It exhibits the highest stability among other dosage forms.^[10]

Orodispersible tablets (ODTs) have gained a good acceptability among people, especially those with swallowing difficulties and young patients.^[11] ODTs are defined by the European Pharmacopeia (EP) as "uncoated tablet intended to be placed in mouth where they disperse rapidly before

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being swallowed. While the FDA recommends for an ODT to be considered as solid oral preparations that disintegrate rapidly in the oral cavity, with an *in vitro* disintegration time of approximately 30 s or less according to the United States Pharmacopeia (USP).^[12,13]

Child-appropriate dosage forms are indicated by easy administration, palatability, and suitable excipients. This facilitates formulation acceptability and medication adherence.^[14,15]

European Medical Agency established a matrix at 2006 which shows the suitability of different dosage forms to population under 18 years. ODT was scored as “preferable acceptability” to pre-school children (2–5 years) and as “drug of choice” from 5 to 18 years.^[16]

In 2008, the World Health Organization (WHO) proposed a shift in pediatric formulation in preferability of solid dosage forms in light of cost and stability problems and shipping difficulties associated with liquid dosage forms. From then, flexible oral dosage forms as ODT have been recommended as pediatric dosage form worldwide.^[17]

These regulations were necessary to consider specific requirements for pediatric populations and help legalization of the processes of formulation, manufacturing, and marketing of pediatric dosage forms.^[18]

In this work, amoxicillin (AM)^[19] as an antibiotic and ibuprofen (IB)^[20] as nonsteroidal anti-inflammatory agents were chosen based on survey from pediatric clinics and hospitals in the Middle East and the rate at which these two medications are prescribed concomitantly for children <5 years for upper respiratory tract diseases and otitis media. The usual dose used is 125 mg AM usually as suspension 3 times daily and IB as syrup contains 100 mg/teaspoonful also 3 times daily. The short elimination half-life of both APIs makes this FCT justified for the proposal of a pediatric preparation to be given 3 times daily.

The aim of this work is to develop a pediatric oral dosage form contains 125 mg AM and 100 mg IB as ODT using design of experiments (DOEs), optimization of selected formula, and preparation and evaluation based on this design. The selection of this combination was based on clinical survey from Iraq and Jordan. 92 pediatric clinics participated in the survey and 65% gave the information that AM is prescribed concomitant with IB for kids under 10 years to treat different upper respiratory tract infections, especially otitis media and tonsillitis. Mainly both drugs are prescribed as suspension.

METHODOLOGY

Materials and equipment

API and all tablet additives were kindly gifted by Hikma® Pharmaceuticals and Dar Al-Dawa® Pharmaceuticals in

Jordan. Tablet hardness tester 8 M basic (DR. SCHLEUNIGER PHARMATRON), double cone mixer (ERWEKA AR 400), dissolution test apparatus (LABINDIA, DS 140000), and high performance liquid chromatography (HPLC) (Finnigan Surveyor) were used for the study.

Formulation and DOE

The formulation contained two APIs, AM (125) mg and IB (100) mg/tablet. In addition to the APIs, six excipients were chosen based on their safety and suitability for pediatric preparation and enhancement of tablet characteristics to meet the criteria of ODT. Mannitol was chosen as diluent in a fixed weight to improve mouth feeling, taste, and for its solubility and wettability.^[21] Aerosil as glidant to improve flowability, especially with direct compression processes^[22] and sodium stearate as lubricant for its higher water solubility than magnesium stearate.^[23]

Sodium starch glycolate (SSG) was chosen as superdisintegrant,^[24] Avicel, as a channeling agent to improve water absorption by tablets^[25] and in low concentration to avoid tablet overweight. Also, sucrose was chosen as sweetener to improve the taste since the tablets are designed for pediatric use.

DoEs are a technique for developing an experimental matrix design that requires specific inputs, measurable outcomes, weighted interests, and experience in reviewing the output. It helps plan the shortest route to improved product performance. Utilization of a well-planned DoE saves supplies, energy, and time and minimizes necessary resources while maximizing product performance.

The concentration of the disintegrant could be crucial factor in time of disintegration of ODT; however, increase concentration reaches sometimes a limit that makes further increase costly and ineffective. Avicel absorbs water more than mannitol which makes its contribution in wetting and DT more effective and sucrose is a natural sugar used to avoid artificial sweeteners for pediatric and its known to be affected by humidity and it does not have good compressibility characters, which makes optimization of its concentration necessary.

Thus, these three excipients were chosen to evaluate the performance of the tablets.

The composition of each formula is illustrated in Table 2. These amounts and concentrations were optimized using the DOE taking the increase of the three mentioned additives linear as – 1 as minimum amount, 0 medium amount, and +1 as maximum amount. Based on that, the program suggested 13 formulas as shown in Table 2. These 13 formulas were prepared and evaluated for physical characteristics and the formula which fulfills the criteria was then adjusted. The criteria were to have DT and wetting time (WT) minimum

Table 1: The composition of the 13 formulas

Ingredient (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
AM	125	125	125	125	125	125	125	125	125	125	125	125	125
IB	100	100	100	100	100	100	100	100	100	100	100	100	100
SSG	25	50	25	50	25	50	25	50	0	0	0	0	25
Avicel	20	20	40	40	0	0	0	0	20	40	20	40	20
Sucrose	0	0	0	0	7.5	7.5	15	15	7.5	7.5	15	15	7.5
Mannitol	100	100	100	100	100	100	100	100	100	100	100	100	100
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4	4
Na stearate	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	333	403	398	423	365.5	390.5	373	398	360.5	380.5	368	388	385.5

SSG: Sodium starch glycolate, AM: Amoxicillin, IB: Ibuprofen

Table 2: Design and respective responses

Formula	SSG (mg/tab)	Avicel (mg/tab)	Sucrose (mg/tab)	DT (sec)	WT (sec)	T _{70%} IB	T _{70%} AM
1	25	20	0	65	100	28	21.7
2	50	20	0	35	58	22	18.8
3	25	40	0	60	65	29	22.8
4	50	40	0	75	70	44	41.5
5	25	0	7.5	73	90	60	53.5
6	50	0	7.5	50	60	30	26.4
7	25	0	15	100	120	67	55.7
8	50	0	15	40	64	51	29.5
9	0	20	7.5	140	156	65	54.3
10	0	40	7.5	107	130	44	41.6
11	0	20	15	140	170	55	48.4
12	0	40	15	115	175	70	52.4
13	25	20	7.5	123	178	82	57

and 70% of both APIs is released in 30 min or less.

Each batch was prepared of 200 tablets. Hardness was controlled during compression process to be optimized to ODT which is $3-3.8 \pm 0.4$ kg/cm².

Ingredients except sodium stearate were weighed and mixed in double cone mixer for 30 min. Then, sodium stearate was added and further mixing continued for extra 5 min. Powder blend was directly compressed using a rotary tablet press (Cadmach® Compression Machine, India) using 9.7 mm flat beveled bisected upper punch and plain lower punch.

The three response factors were WT, DT, and time required to dissolve 70% of drug (T_{70%}). Table 1 shows the composition of the suggested 13 formulas.

Evaluation of the prepared tablets

The 13 formulas were evaluated according to USP requirements. Weight and weight variation, drug content,

WT, DT, and drug release and drugs dissolution were all evaluated.

Weight and weight variation were tested by choosing random sample of 20 tablets of each formula, weighing each alone using balance (OHAUS GOLO SERIES) and calculation of average WT and \pm SD.

WT was tested for each formula using the filter paper and Petri dish.^[26] In each Petri dish, 10 ml D.W were put and a folded filter paper was soaked. Then, the tablet was put above. Time when the upper surface is fully wetted was recorded in seconds. The test was repeated 3 times for each formula and average time and \pm SD were calculated.

DT was tested by USP disintegrator (Galvano Scientific DT-122 model). Three tablets were put each time in D. W and average time \pm SD was recorded in seconds.

Drug APIs content of tablets was tested by modifying the USP monograph of both drugs. 20 tablets (theoretically

contain 2 g IB and 2.5 g of AM) were crushed and an amount of powder corresponding to content of 1 g IB and 1.25 g AM was weighed. APIs were extracted with 60 ml chloroform and 60 ml alcohol in a separatory funnel and shaken for 20 min; then, layers were separated. The aqueous layer contained AM and the chloroform layer contained the IB. Chloroform layer was evaporated and the residue was dissolved in 50 ml of 95% ethanol. Serial dilutions were made by the mobile phase of the method specified, and the amount of IB was calculated.

The aqueous layer was diluted to get suitable concentration of AM and measured by the same HPLC method.

Dissolution test (for the optimized formula) was performed later using USP Type II apparatus. Six tablets were put in the vessels each containing 900 of phosphate buffer pH 6.8 and temperature $37 \pm 0.5^\circ\text{C}$. Samples were taken in time schedule (5, 10, 20, 30, 40, 50, and 60 min), filtered and concentration of both APIs was determined using a validated method above. Percentage drug release was plotted against time in minutes to get the dissolution profile.

Statistical analysis was used, all tested values are expressed as mean \pm SD; the response factors calculated by DoE were analyzed on CI 95% in high and low level.

RESULTS AND DISCUSSION

The three response factors for the suggested formulas (F1-F13) are given in Table 2.

It was observed that the DT of tablet depends on the SSG, Avicel, and sucrose which expressed in the given formula.

$$DT = 65.83 - 1.79 \times SSG + 1.31 \times AVECIL + 12.54 \times SUCROSE + 0.06 \times SSG \times AVECIL - 0.05 \times AVICEL^2 + 0.53 \times SUCROSE^2$$

It very clear from the equation and the figure that the Avicel is having positive impact on the DT (it increases the DT time)

while SSG is having negative impact (it decreases the DT). Figure 1 shows this effect.

As far as wetting is concern, it depends on Avicel and SSG. The WT increased on increasing the Avicel concentration probably due to facilitation of water entrance to the interior of the tablet. On increasing the concentration of SSG, it shows mixed type of response. Higher concentration of SSG reduces the WT as shown in Figure 1b.

$$\text{Wetting} = 46.614 + 3.345 \times AVICEL + 14.37 \times SUCROSE + 0.0560 \times SSG \times AVICEL + 0.104 \times AVICEL \times SUCROSE - 0.025 \times SSG^2 - 0.096 \times AVICEL^2 - 0.601 \times SUCROSE^2$$

For drug release and dissolution expressed as time to 70% of drug release, the release of IB depends on the Avicel, SSG, and sucrose. The increase in the percentage of Avicel decreases the percentage release of IB, (in other words, it takes longer time to release 70% of the drug). The increase in the SSG concentration decreases the time to release 70% of the drug. Figures 3a and b show this effect. This may be attributed to the fact that SSG fastened disintegration and deaggregation of particles that made the drug released easier. While, possibly the higher concentration of avicel may trap some drug particles and delayed its release.

When predict the effect of sucrose with Avicel, increasing sucrose delayed the release and Avicel enhanced it. This may suggest some kind of physical interaction that changed the previous response.

The release of AM depends on the Avicel and SSG. Similar response was observed, as the percentage of Avicel decreases, the percentage release of AM requires less time, (in other words, it takes longer time to release 70% of the drug, if the percentage of Avicel is increased from 5 mg to 50 mg). The increase in the SSG concentration decreases the time to release 70% of the drug. AM is more polar than IB. This suggests that the effect did not depend on hydro-/lipo-philicity of the active ingredients; rather,

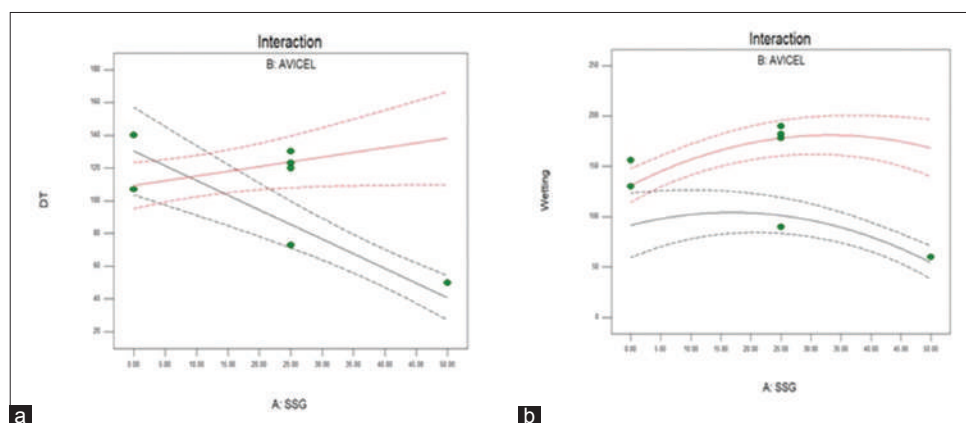


Figure 1: Prediction of the effect of sodium starch glycolate and Avicel on DT (a) and wetting time (WT) (b).

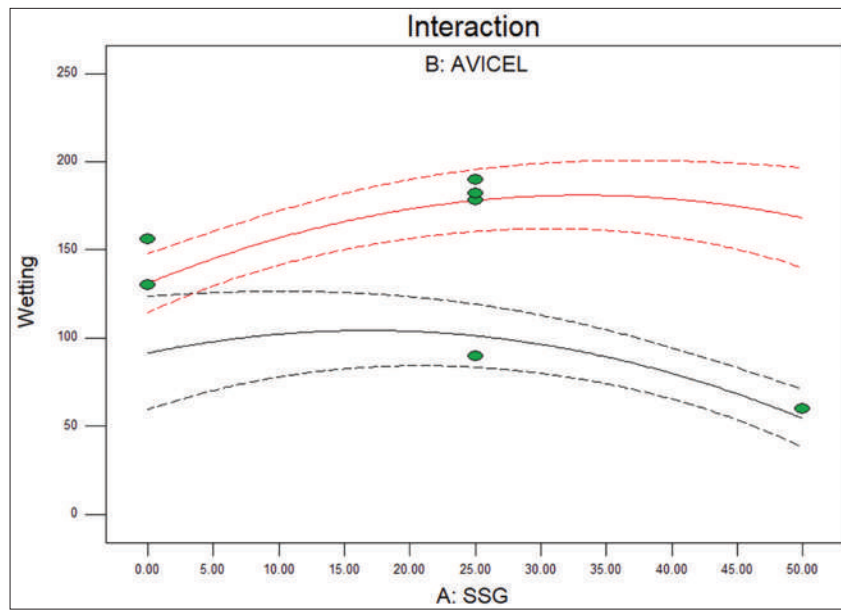


Figure 2: Prediction of effect of SSG and Avicel on WT

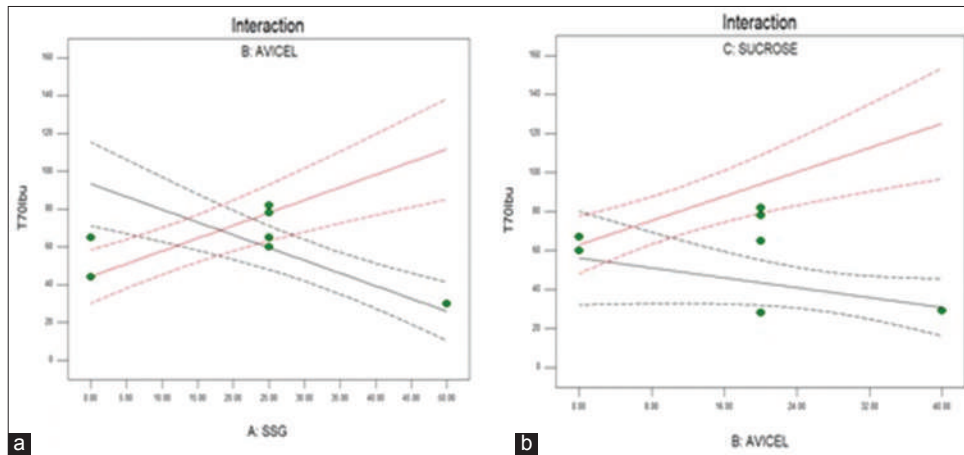


Figure 3: Prediction of the effect of Avicel and sucrose (a), SSG and Avicel (b) on $T_{70\%}$ release of IB

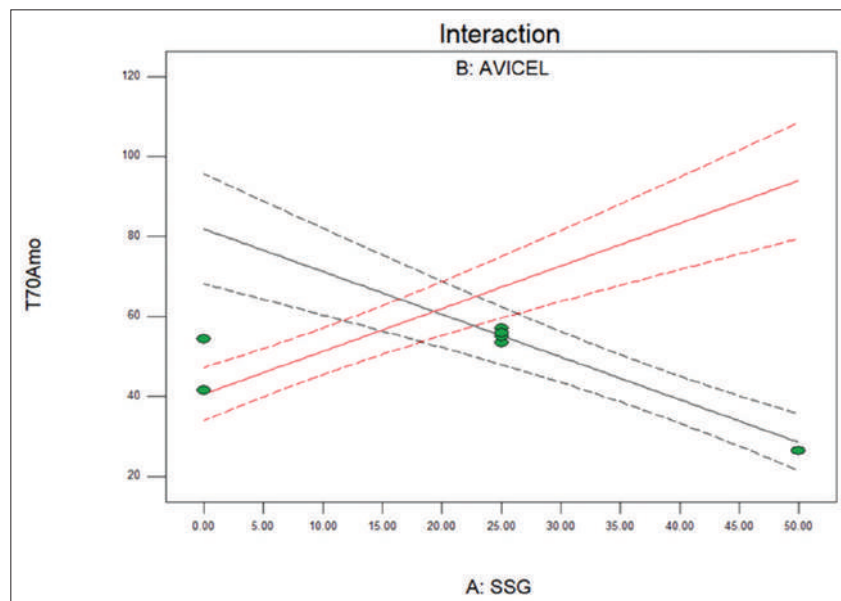


Figure 4: Prediction of the effect of SSG and Avicel on $T_{70\%}$ release of AM

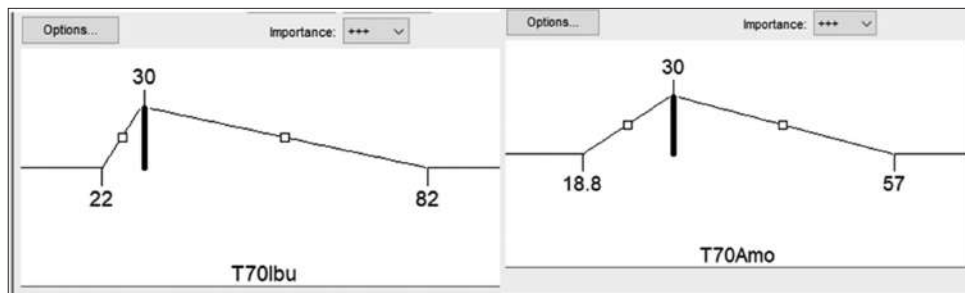


Figure 5: Optimization of drug release for 30 min (right AM, left IB)

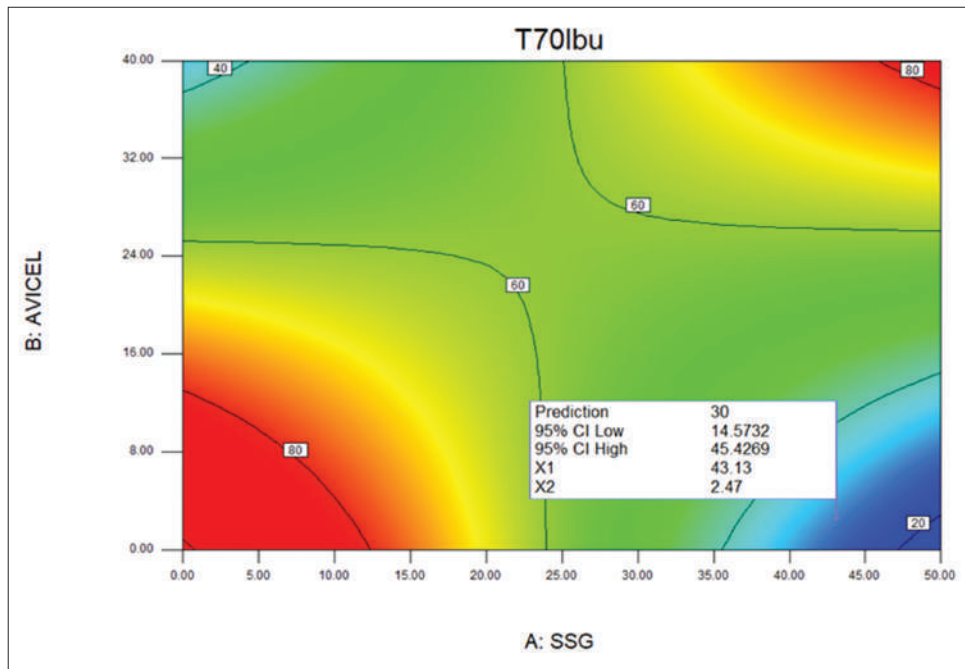


Figure 6: Desirability figure of SSG and Avicel in addition to the optimum time of release of IB

Table 3: Results of tablets evaluation (F1-F6)

Formula	F1	F2	F3	F4	F5	F6
Weight/mg	339±7	408±8	400±5	419±6	369.5±7	390.5
Wetting time/sec	100±3	58±3	65±4	70±3	90±4	60±3
D.T	65±4	35±2	60±2	75±4	75±4	50±7
Percent dissolution at 20 min (IB)	40±3.1	67±6	45±5.2	35±6	35±6.8	55±6.3
Percent dissolution at 20 min (AM)	67±8.7	78±6	6745±5.1	45±8	42±4.2	61±4.8
Drug content (%) AM	94.4	102.4	95.4	102.5	100.9	108
Drug content (%) IB	95	103	96	94.5	98	102

Table 4: Results of tablets evaluation (F7-F13)

Formula	F7	F8	F9	F10	F11	F12	F13
Weight/mg	367±5	398	400.5±5	385.5±10	371±5	383±4	335±8
Wetting time/sec	120±8	59±2	156±5	130±5	170±3	175±5	180±4
D.T	100±5	40±4	140±3	107±4	140±5	115±3	120±3
Percent dissolution at 20 min (IB)	22±3.1	45±5.2	18±4.7	25±4.9	14±5.1	22±2.6	22±2.6
Percent dissolution at 20 min (AM)	26±4.5	55±5.2	30±6.4	28±1.4	28±1.4	36±4.3	36±4.3
Drug content (%) AM	102.8	105	103	112	96	103	107
Drug content (%) IB	99	100.9	98.5	105	93	97	102

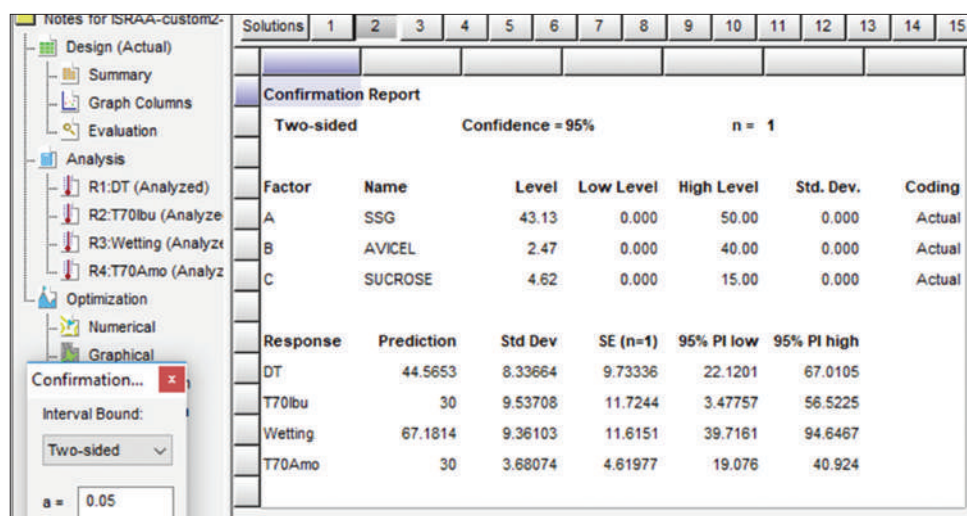


Figure 9: Confirmation report of optimization by DOE

AM 125 mg, IB 100 mg, mannitol 100 mg, aerosil 4 mg, Na stearate 4 mg, SSG 43.13 mg, Avicel 2.47 mg, and sucrose 4.62 mg.

For practical preparation of the formula, SSG was taken as 43, Avicel as 2.8, and sucrose 4.7 mg/tab.

A batch of 200 tablets was prepared and evaluated using same methods mentioned and the results of evaluation are showed in the following Table 3.

These results showed close values to the predicted results according to the design. WT and DT are short and fit largely the criteria of ODT. Drug dissolution can be achieved with $\frac{1}{2}$ h which is also suitable for ODT.

This proves that the use of this design and formulation was successful for this combination. On large scales, this method could save time and cost to bring the best composition of a formula.

CONCLUSION

Using DOE to predict suitable composition of a formula which contained a combination of IB and AM as APIs for pediatric use was successful in designing the formula that fitted the criteria of ODT tablets.

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