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Research Article

DEVELOPMENT AND CHARACTERIZATION OF ANTIBIOTIC ORODISPERSIBLE TABLETS

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ABSTRACT

The goal of this project is to formulate oro-dispersible tablet of Azithromycin that is intended to disintegrate rapidly into the oral cavity and form a stabilized dispersion. A direct compression method was failed to formulate dispersible tablet of Azithromycin so wet granulation method was used. In preliminary study different superdisintegrant croscarmellose sodium (CCS), sodium starch glycolate (SSG) and crospovidone (CPVP) were evaluated for weight variation, content uniformity, hardness, disintegration time, and friability of tablets. In all the formulations water was used as a binding agent to attain hardness. Avicel was used as diluents. Aspartame was used as a sweetening agent. Magnesium stearate and Aerosil were used as lubricant and glidant respectively. FT-IR studies were utilized to obtain the compatibility of the drug and excipients. The simplex lattice design was utilized using amount of intragranular concentration of superdisintegrants, sodium starch glycolate(A), cros-carmellose sodium(B) and crospovidone(C) were selected as independent variable. The Hardness (R_1), Disintegration time (R_2), Friability (R_3) and Wetting time (R_4) were selected as dependent variables. A total of 11 formulations with 4 replicas was obtained and optimized. From response surface plot of disintegration time, wetting time, friability and hardness it was found that lower disintegration time of tablets could be obtained when C and B are kept at optimum level. Stability study of final batch showed no significant changes in tablet properties.

Key words: Azithromycin; Disintegration time; FT-IR; Oro-dispesible tablet; Optimization; Simplex lattice; wetting time.

INTRODCUTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance.

It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Mouth Dissolving Tablet (MDT) is one among such approaches.[1]

Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms.

But one important drawback of such dosage forms is Dysphagia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a no. of pathological conditions including stroke, parkinson's disease, neurological disorders, AIDS etc. Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally disabled persons, Unavailability of water.[2]

To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.[3]

In present research work, dispersible tablet of Azithromycin is formulated using granulation technique.Azithromycin is an advanced-generation; broad-spectrum antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB)[4], group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients. Azithormycin has slightly bitter test and has half life of 68 hrs and has poor water solubility. So in case of acute bacterial exacerbation of chronic bronchitis (AECB) group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections it require immediate release of drug from the dosage form, which make Azithromycin suitable candidate for dispersible tablets.[5]

MATERIALS

Azithromycin was obtained as a gift sample from KAPL-Bangalore. Micro Crystaline Cellulose(Avicel), Sodium Lauryl Sulphate, Aerosil, Magnesium Stearate and Aspartame were purchased from S.D. Fine chemicals. Croscarmellose sodium, Sodium starch glycolate and crospovidone also were obtained as a gift sample from Cadila Pharmaceuticals Limited (Dholka, Ahmedabad). All other chemicals were of analytical grade.

Preparation of oro-dispersible dissolving tablet of Azitromycin

Dispersible tablet of Azithromycin were prepared by granulation according to the formula given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the granules were prepared with intragranular ingredients using water as a binder passing lumps through # 8 mesh. Then extragranular ingredients were weighed and mixed in geometrical order with prepared granules and compressed into tablet of 200 mg using 8 mm flat punches on multipunch tablet compression machine, (Karnavati Machinery Co. Pvt. Ltd., Ahmedabad, India). A batch of 50 tablets was prepared for each of the designed formulations.[6]

Evaluation of tablet characteristics

Tablets were evaluated for weight variation, drug content uniformity, friability, disintegration time. Drug content was analyzed using U.V spectrophotometer (Shimadzu 1700 UV/Visible double beam Spectrophotometer, Japan) at 210 nm. Tablet friability was

measured using Roche friabilator (Electrolab, EF-2 (USP) for 4 mins at 25 RPM. Three tablets were selected randomly from each batch and tested for hardness using Pfizer hardness taster, and disintegration time was determined using USP disintegration test apparatus model (ED-2L, Electrolab) at 24 ± 20^{0}C.[7]

In-vitro dissolution

Dissolution studies of all tablets were performed using automated programmable dissolution tester (Paddle type, TDT-08L, Electrolab, India). Tablets were added to the 900 ml of 0.1 N HCl at 37°C ± 0.5°C, which was stirred with a rotating paddle at 50 rpm. At timeintervals of 5 minutes, 5ml samples were withdrawn and equal volume of fresh medium prewarmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test . Assay carried out using U.V. spectrophotometer (Shimdzu 1700 UV/Visible double beam Spectrophotometer, Japan) at 210nm.[8]

Stability study

The stability of samples was monitored up to 3-month at ambient temperature and relative humidity (30 °C / 65% RH). Periodically samples were removed and characterized for disintegration time, hardness, drug content and dispersion time.[9]

Simplex design for optimization

A simplex lattice design[10] was adopted to optimize the formulation variables and experimental trials are performed at all 9 possible combinations. The amount of intragranular concentration of superdisintegrants, sodium starch glycolate(A), croscarmellose sodium(B) and crospovidone(C) were selected as independent variable. The Hardness (R_1), Disintegration time (R_2), Friability (R_3) and Wetting time (R_4) were selected as dependent variables.[11]

RESULTS AND DISCUSSION

Bulk densities and tapped densities of various formulations were found to be in the range of 0.41±0.006 to 0.50±0.007 (g/cc) and 0.50±0.03 to 0.58±0.003 (g/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Hardness of preliminary batches prepared using three different superdisintigrants were found 3 to 5 kg/cm2. The average weight of the tablet is approximately in range of 197±0.92 to 202.5±0.98. The average friability of all the formulations lies in the range of 0.30±0.0057% to 0.51±0.0057 which was less than 1% as per official requirement of IP. The average wetting time of all the formulations was obtained in the range of 11-24 seconds. disintegration time of prepared tablets were in the range of 12.66±0.5773 to 30.33±0.5773seconds. Drug contents were in acceptance limits. Formulations F1, F2, F6, F8, F9 and F10 showed more than 90% of drug release within 30 min, whereas in formulation F3, F4, F5, F7 and F11 showed 75-90% of drug release within 30 min.[12]

Using simplex lattice design from the regression analysis and 3-D surface plot it is obtained that CPVP with combination of other two super-disintegrants is showing good decrease in hardness. In case DT, CPVP with combination of CCS is very effective to decrease the DT which is desirable. While in case of friability CPVP with combination of CCS and SSG very effective to decrease the Friability which is desirable. And in case of wetting time CPVP and CCS are effective to decrease the Wetting Time which is desirable. ($P<0.0001$)[13]

Hardness R_1= +3.66*A+3.66*B+3.77*C-4.68*A*B-8.64*A*C-8.64*B*C+75.04*A*B*C

Disintegration time R_2= +30.33*A+22.66*B+17.00*C+41.32*A*B-16.76*A*C-58.70*B*C-14.49*A*B*C

Friability R_3= +0.49*A+0.34*B+0.34*C+0.86*A*B-0.70*A*C-0.76*B*C-3.96*A*B*C

Wetting Time R_4= +24.66*A+18.00*B+15.33*C+51.36*A*B-28.62*A*C-8.70*B*C-177.12*A*B*C

Three months stability study at ambient temperature and relative humidity (30 °C / 65% RH) of formulation F10 revealed that the formulation was stable and there were no significant changes observed for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the developed formulation has good stability.

CONCLUSION

Amongst the various combinations of diluents and disintegrants used in the study, tablets that were formulated (wet granulation) using Crospovidone (10%), crosscarmelose sodium and sodium starch glycolate (each 5%) exhibited quicker disintegration of tablets than compared to those other combination of disintegrants in different concentration. The effectiveness of super-disintegrants was in order of CPVP>CCS>SSG.Formulation F10 was the optimized formulation having least disintegration time as well as other parameters were in acceptable range.

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Table 1 Formulation using simplex lattice design

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}
Intragranular											
Azithromycin	100	100	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	5	-	30	10	30	-	30	-	-	5	20
Crosscarmellose sodium	20	30	-	10	-	30	-	-	-	5	5
Crosspovidone	5	-	-	10	-	-	-	30	30	20	5
Avicel	38	38	38	38	38	38	38	38	38	38	38
Sodium lauryl sulphate	2	2	2	2	2	2	2	2	2	2	2
Extragranular											
Aerosil	5	5	5	5	5	5	5	5	5	5	5
Magn. Stearate	5	5	5	5	5	5	5	5	5	5	5
Aspartame	20	20	20	20	20	20	20	20	20	20	20
Total	200	200	200	200	200	200	200	200	200	200	200

Table 2: Design summary response data

Run	SSG	CCS	CPVP	Hardness	DT	Friability	%CPR
1	5	20	5	0.33±0.5773	20.33±0.5773	0.43±0.0264	19.33±0.5773
2	-	30	-	3.66±0.5773	22.66±0.5773	0.34±0.0173	18±0.0000
3	30	-	-	3.66±0.5773	30.33±0.5773	0.49±0.0173	24.66±0.5773
4	10	10	10	4±0.0000	19±1	0.47±0.0100	14.33±0.5733
5	30	-	-	3.66±0.5773	30.33±0.5773	0.49±0.0173	24.66±0.5773
6	-	30	-	3.66±0.5773	22.66±0.5773	0.34±0.0173	18±0.0000
7	30	-	-	3.66±0.5773	30.33±0.5773	0.49±0.0173	24.66±0.5773
8	-	-	30	3.66±0.5773	17±1	0.34±0.0173	15.33±0.5773
9	-	-	30	3.66±0.5773	17±1	0.34±0.0173	15.33±0.5773
10	5	5	20	3±0.0000	12.66±0.5773	0.30±0.0057	11.33±0.5773
11	-	5	5	3.33±0.5773	27.66±0.5773	0.51±0.0057	21±1

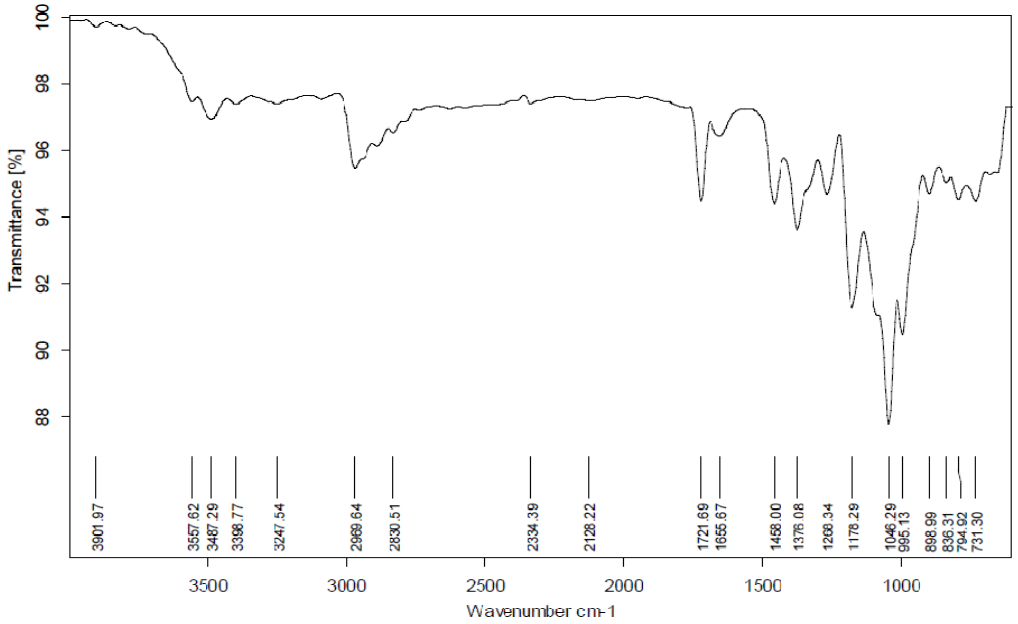

Fig. 1: FT-IR spectra of pure Azithromycin

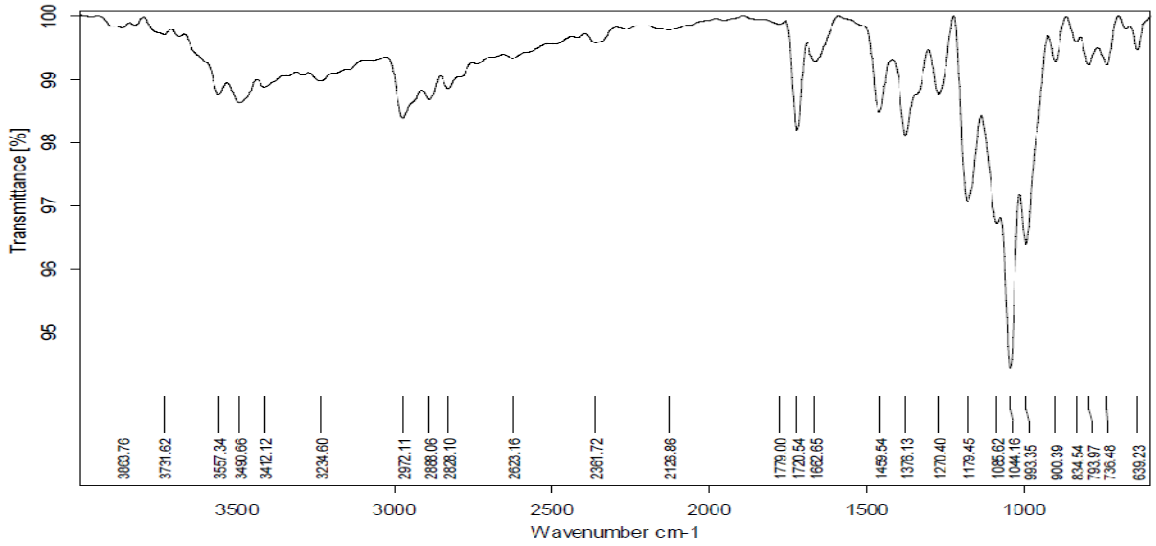

Fig. 2: FT-IR spectra of pure Azithromycin+ SSG

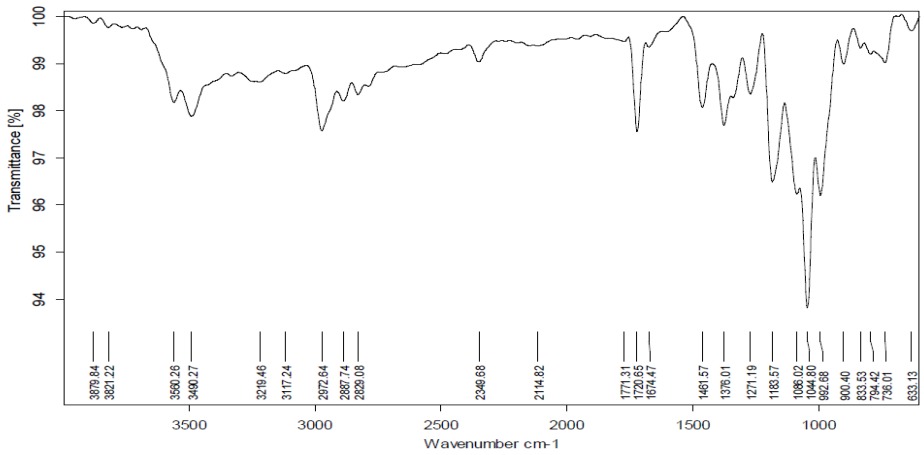

Fig. 3: FT-IR spectra of pure Azithromycin+CCS

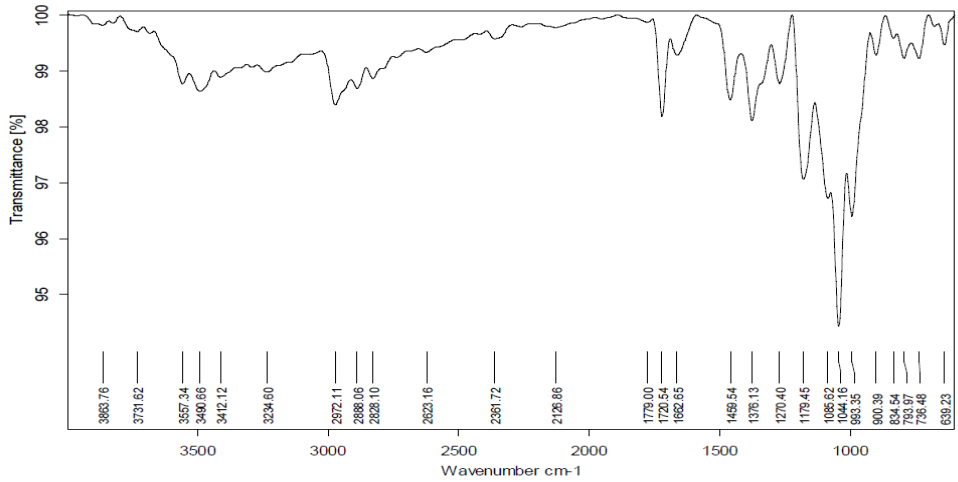

Fig. 4: FT-IR spectra of pure Azithromycin+ Crosspovidone

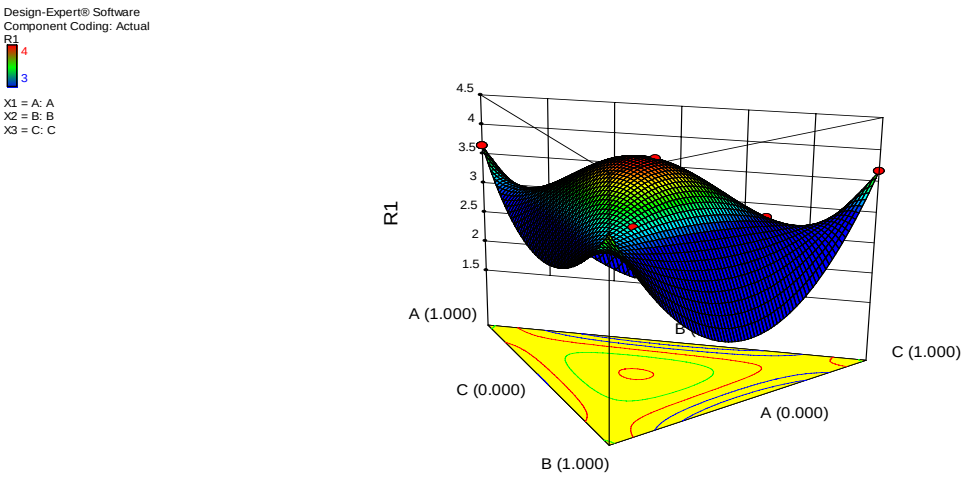

Fig. 5: 3-D graph showing effect of SSG, CCS and CPVP on Hardness (R_1)

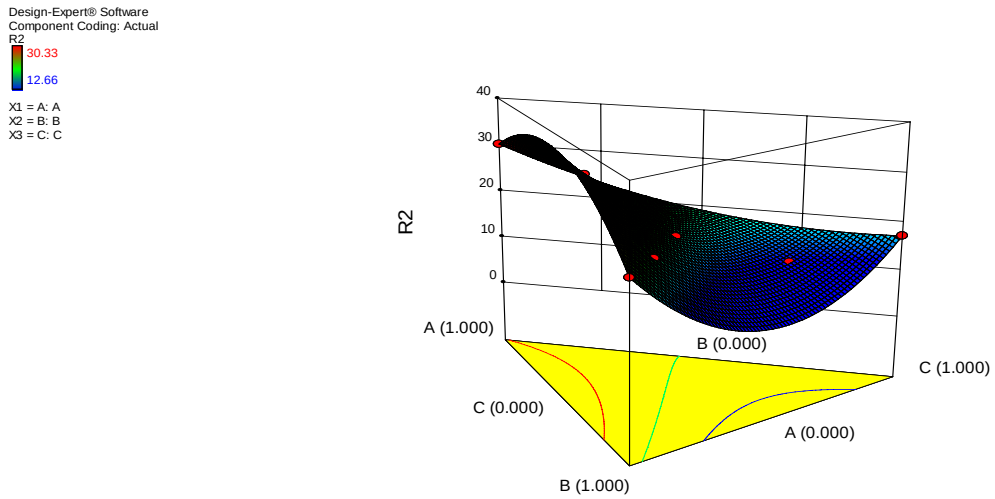

Fig. 6: 3-D graph showing effect of SSG, CCS and CPVP on Disintegration Time (R_2)

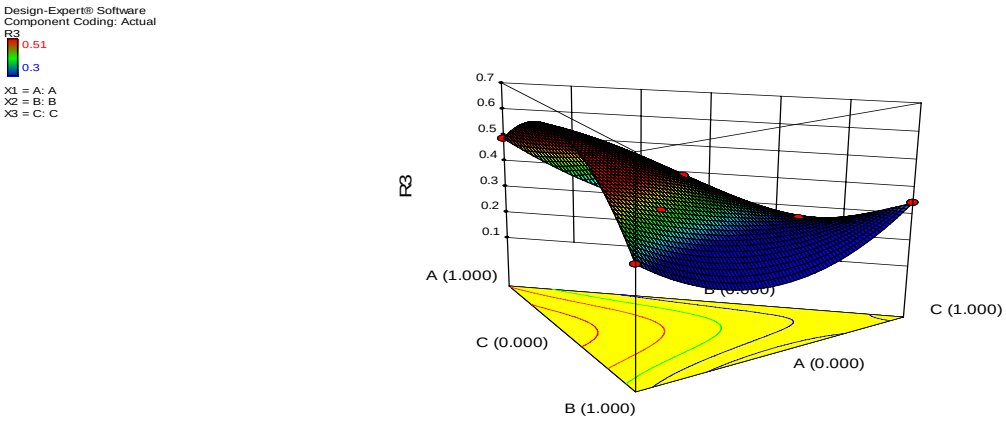

Fig. 7: 3-D graph showing effect of SSG, CCS and CPVP on Friability (R_3)

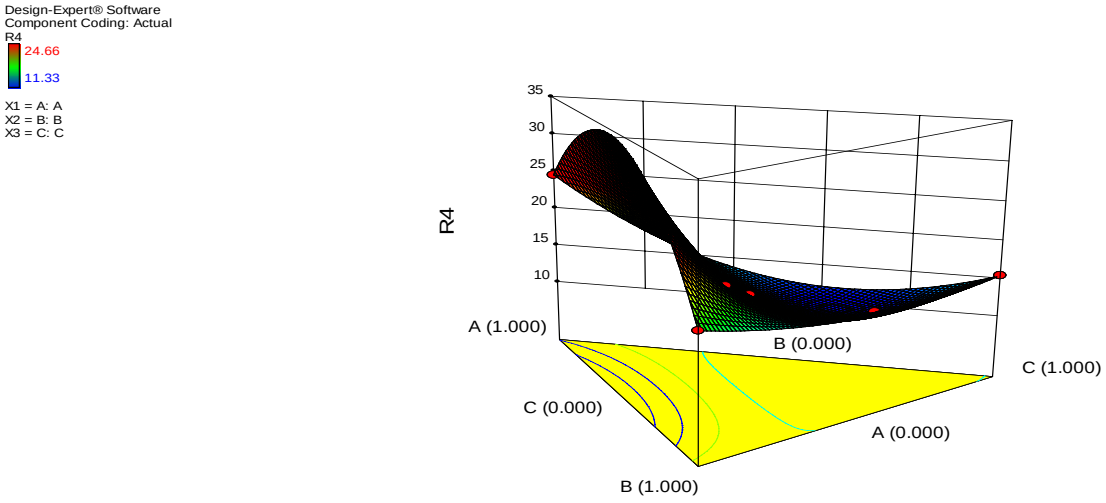

Fig. 8: 3-D graph showing effect of SSG, CCS and CPVP on Wetting time (R_4)

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