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Full Length Research Paper

Optimization of environmental and nutritional conditions to improve growth and antibiotic productions by *Streptomyces* Sp. Isolated from Saudi Arabia Soil

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Abstract

The purpose of the present study was to optimize the environmental and nutritional conditions for the isolate *Streptomyces* sp. MS-266 Dm4 to improve antibiotic production. The results showed that the highest antimicrobial activity were obtained after 7 days of growth under shaking conditions at initial pH 6 and temperature 30°C. Starch (2g/100ml) was found to be the most suitable carbon sole source for optimum growth and antibiotic productions. Peptone (0.04g/100ml) and NaNO3 (0.2g/100ml) were found to be the most suitable nitrogen sole source for antibiotic productions and optimum growth, respectively. The effect of different concentration of mineral salts, were investigated. The maximum antibiotic production by *Streptomyces* sp. MS-266 Dm4 was obtained in a medium of the following composition (g/l): Soluble starch 2.0, peptone 0.04, K_2HPO_4 0.2, $MgSO_4.7H_2O$ 0.15, KCL 0.05 and $FeSO_4.5H_2O$ traces, at pH 6.0 incubation period was seven days under shaking conditions.

Keywords: *Streptomyces* sp, Optimization, antimicrobial activity.

INTRODUCTION

The ability of Actinomycetes especially *Streptomyces* sp. to produce antibiotics is unlimited (Enomoto *et al*., 2000; Guangying *et al*., 2005; Ilic` *et al*., 2005; Kim *et al*., 2005; Jeong *et al*., 2006; Xie *et al*., 2007). Therefore, *Streptomyces* sp. widely recognized as industrial antibiotic producing organisms (Ningthoujam *et al*., 2009; Rajput *et al*., 2012; Singh *et al*., 2012). Antibiotics production by *Streptomyces* sp. it is possible to increase it or lose it completely under different conditions. Environmental factors and cultural nutrition have been proven to affect growth and the production of antimicrobial agents of different streptomycete isolates by many researchers (Farid *et al*.,2000; Jonsbu *et al*., 2000; Theobald *et al*., 2000; Hassan *et al*., 2001; Gubte and Kulkarni, 2002; Jonsbu *et al*., 2002; Padma *et al*., 2002; El-Naggar *et al*., 2003; Gesheva *et al*., 2004; Kiviharju *et al*., 2004; Venkateswarlu *et al*., 2004; AL-Zahrani, 2007). Also, adding different mineral salts, such as K_2HPO_4, $MgSO_4$ and KCl play a major role in the growth and in production of antimicrobial agents (Ueda *et. al*., 1997; Atta, 1999 and Aman, 2001).

A culture of streptomycetes which is identified as *Streptomyces* sp. MS-266 Dm4 (Ababutain *et al*., 2012a) was found to produce lincomycin antibiotic (Ababutain *et al*., 2012 b). This antibiotic exhibited antibacterial and Insecticidal activity against gram positive, gram negative bacteria and *Culex pipiens* mosquito (Ababutain *et al*., 2012a). The aim of this study was to determine the best nutritional conditions for optimal growth and antibiotic activity of *Streptomyces* sp. MS-266 Dm4 isolated from Saudi Arabia soil.

MATERIALS AND METHODS

Microorganism

The strain *Streptomyces* sp. MS-266 Dm4 was isolated from Dammam, Saudi Arabia soil (Ababutain *et al*., 2012a). The test organism was *Bacillus cereus.*

Effect of the environmental condition

This includes the effects of incubation period, incubation temperatures and pH values. The dry weight was investigated and antimicrobial activity was tested by using the classical diffusion methods described by (Betina, 1983). Hundred ml of Starch nitrate broth medium were distributed among conical flasks with 250ml capacity. The flasks were sterilized, inoculated with 10 ml of *Streptomyces* sp. MS-266 Dm4 previously grown for 3 days in medium contained: yeast extract 10g, dextrose 10g, and tap water1000 ml with a pH of 6.8. Then, cultures were incubated at 30℃ under static or shaken conditions separately. Cultures were removed at various intervals of incubation periods (3, 5, 7 and 9 days). After adjusting the incubation period the optimum growth temperature was studied. After inoculation, cultures were incubated at different temperatures (20-30-40-45- and 50° C). To study the effect of initial pH value, 100 ml aliquots of medium were adjusted to initial pH values (3-11), using 1N HCl or NaOH. At the end of incubation period, the dry weight and antibacterial activity were estimated.

Effect of nutritional conditions

This includes the effect of different carbon and nitrogen sources. *Streptomyces* sp. MS-266 Dm4 was initially grown in inoculation medium contained: yeast extract 10g, dextrose 10g, and tap water1000 ml with a pH of 6.8. The medium was sterilized, inoculated with *Streptomyces* sp. MS-266 Dm4 for 3 days at 30℃ on a rotary shaker of 200 rpm. After growth 10 ml of *Streptomyces* sp. MS-266 Dm4 culture was transferred into the production medium contained the following components (g/100ml): starch 2.0, $NaNO_3$ 0.2, K_2HPO_4 0.1, $MgSO_4.7H_2O$ 0.05, KCL 0.05 and $FeSO_4.5\ H_2O$, traces. To study the influence the carbon sources different carbohydrates such as (glucose 2.1, galactose 2.1, fructose 2.1, maltose 2.0, sucrose 2.0, natural starch 2.3, and soluble starch 2.3) were added with equimolecular amount to the production medium in which starch was omitted. Influence of different concentrations of the best carbon source on the growth and antibacterial activity were estimated.

Nitrogen sources (peptone 0.2, beef extract 0.3, $(NH_4)_2SO_4$ 0.155, KNO_3 0.24 and urea 0.073) were added with equimolecular amount to the growth medium containing the optimal carbon source in suitable concentration, $NaNO_3$ was omitted. Influence of various concentrations nitrogen source on the growth and antibiotic production was studied. The mineral salts (K2HPO4, MgSO4.7H2O and KCL) were supplemented in different concentrations to basal production medium.

RESULTS

Effect of the environmental condition

Table (1) and figure (1) show that the maximum antimicrobial activity was attained after seven days of incubation under shake conditions. *Streptomyces* sp. MS-266 Dm_4 produced the antimicrobial agent after three days of incubation against gram positive bacteria (*B. cereus*), in which the inhibition zone size was (26 mm) under shaken conditions, while its (17 mm) under static conditions after five days of incubation. In addition, antimicrobial activity increased by increasing the incubation period up to seven days to rich 32mm in increase of 12.5%. The effect of incubation period on the dry weight under shaken condition was illustrated in (Table, 1).

Table (2) and figure (2) show the relationship between antimicrobial activity, Dry weight and incubation temperatures. The incubation temperature 30℃ was the best temperature for the growth and antimicrobial agent was produced by *Streptomyces* sp. MS-266 Dm_4. The inhibition zone size was 32 mm against (*B. cereus*) followed by inhibition zone size (25, 19 mm) in 40℃ and 45℃ respectively. The less antimicrobial activity produced in incubation temperature 20℃ in which the inhibition zone size was (15 mm). In incubation temperature 50℃ the antimicrobial activity prevented.

Table (3) and figure (3) show that the pH 6.0 is the most suitable pH values for the antimicrobial activity, which gave 28mm inhibition zone. Moreover, the pH 8.0 was the least values, which gave 20 mm inhibition zone. On other hand pH values used in this study (3-11) had less affect on the dry weight and it was between 0.3-0.5 g/100ml.

Effect of nutritional conditions

Effect of supplying certain nutritional requirements on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 was studied. Table (4) and figure (4) show the effect of adding different carbon sources on the dry weight and antimicrobial activity of *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*. The utilization of the tested carbon sources by isolate No. 4 for antibiotic production was found to be in the following descending manner: soluble starch = Glucose > fructose = galactose. In addition, the result shows that isolate No.4 can’t utilizes sucrose and maltose for antibiotic production. While, the natural starch prevents the antimicrobial activity and the growth. The highest dry weight appeared with the addition of soluble starch.

Table (1) The effect of different incubation periods on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus* under shaken and static conditions.

Incubation period(days)		Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
3	Shaken	26	0.7
	Static	0.0	
5	Shaken	28	0.5
	Static	17	
7	Shaken	32	0.9
	Static	0.0	
9	Shaken	25	0.7
	Static	0.0	

Figure (1) The effect of different incubation periods on the productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm4 against B. cereus under shaken and static conditions.

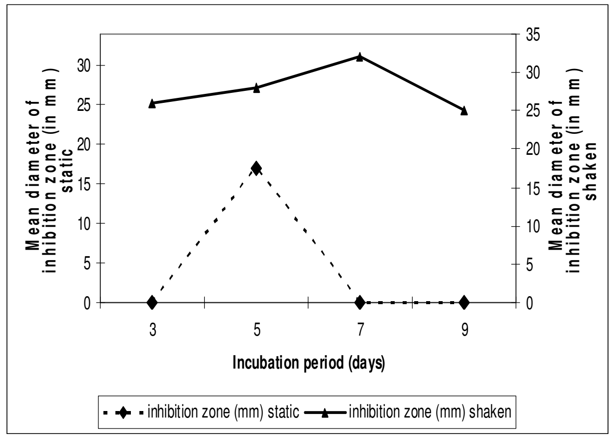


Table (2) The effect of different incubation temperatures on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

Incubation temperatures (°C)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
20	15	0.3
30	32	0.9
40	25	0.4
45	19	0.4
50	0.0	0.4

Figure (2) The effect of different incubation temperatures (°C) on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

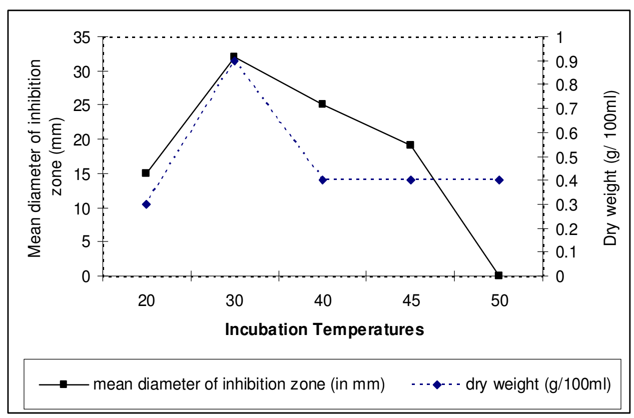


Table (5) and figure (5) show the effect of adding different concentrations of soluble starch on the dry weight and productivity of antimicrobial agents by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*. The concentration 4.0 g/100ml was the best.

Effects of supplying different nitrogen sources with different concentrations on the dry weight productivity of antimicrobial agent were studied. Among the nitrogen sources tested, the peptone was the best for the productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*, Whereas $NaNO_3$ was the best for the dry weight Table (6) and figure (6). The other nitrogen sources used in this study prevented the antimicrobial activity and reduced the dry weight. The result showed that the *Streptomyces* sp. MS-266 Dm_4 was able to grow without nitrogen sources, dry weight was 0.3 g/100ml.

Among the concentration of peptone tested, 0.04g/100ml was the best concentration for the productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*, whereas the concentrations (0.20 -0.45) g/100ml were the best for the dry weight, table (7) figure (7).

The effect of supplying different concentrations of K_2HPO_4 is illustrated in figure (8) and table (8). It is obvious that maximum antibiotic production and dry weight was recorded in presence of 0.2 g/ 100ml. The effect of supplying different concentrations of $MgSO_4$ is

Table (3) The effect of different pH values on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

Values of pH	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
3	25	0.3
4	25	0.4
5	26	0.3
6	28	0.5
7	21	0.4
8	20	0.5
9	25	0.5
10	23	0.5
11	22	0.4

Figure (3) The effect of different pH values on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

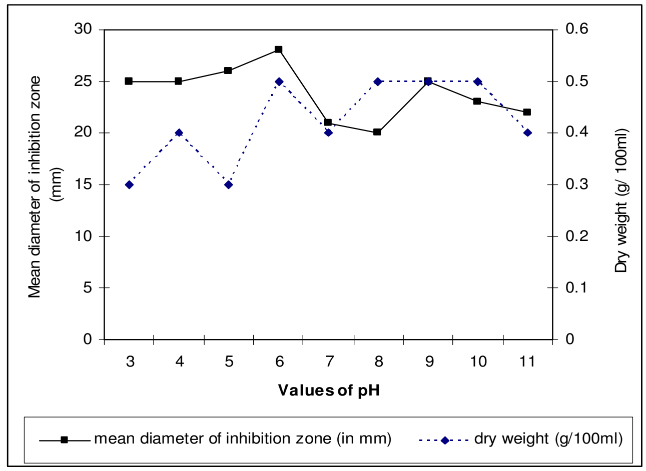
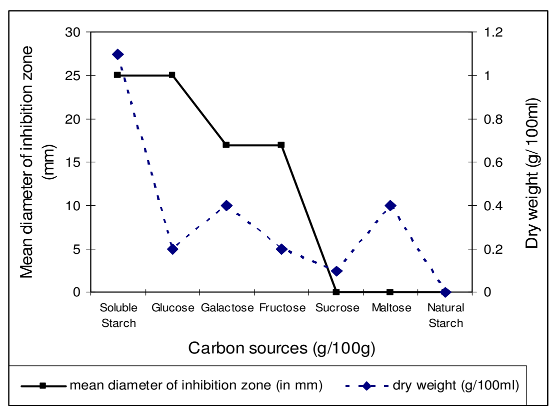


Table (4) The effect of different carbon sources on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm4 against *B. cereus.*

Carbon sources (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
Soluble Starch	25	1.1
Glucose	25	0.2
Galactose	17	0.4
Fructose	17	0.2
Sucrose	0.0	0.1
Maltose	0.0	0.4
Natural Starch	0.0	0.0

Figure (4) The effect of different carbon sources on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm4 against *B. cereus.*



illustrated in figure (9) and table (9). It is clear that maximum antibiotic production was recorded in presence of 0.15 g/100ml. However, the dry weight in lower concentrations of $MgSO_4$ (0.05, 0.08) was higher by 1.7 %. The effect of supplying different concentrations of KCl is illustrated in figure (10) and table (10). It is clear that maximum antibiotic production and dry weight was recorded in presence of 0.05 g/ 100ml.

DISCUSSION

Optimization environmental and nutritional conditions to improve antibiotic productions by *Streptomyces* Sp. which was identified and found to produce lincomycin antibiotic (Ababutain *et al*., 2012 a,b) were estimated. Different environmental conditions such as pH, temperature and incubation period were studied. Adding different nutrients includes carbon, nitrogen sources and mineral salts in various concentrations were studied.

Maximum growth and biosynthesis was occurred at the end of an incubation period of seven days on Starch-nitrate agar medium. This result was identical to the results of (Hassan *et al*., 2001; Venkateswarlu *et al*., 2004; AL-Zahrani 2007). Whereas, five days incubation period was found to be the best by many researchers (Ryoo *et al*., 1997; Holtzel *et al*., 1998; Atta, 1999). In addition, EL-Naggar *et al*., (2003) were found that the

Table (5) The effect of different concentration of soluble starch on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

Concentration of Soluble Starch (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
1.0	20	0.39
1.5	22	0.52
2.0	24	0.59
2.5	21	0.55
3.0	20.5	0.55
3.5	19.5	0.49
4.0	19	0.49
4.5	19	0.48
5.0	17	0.41

Figure (5) The effect of different concentration of soluble starch on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

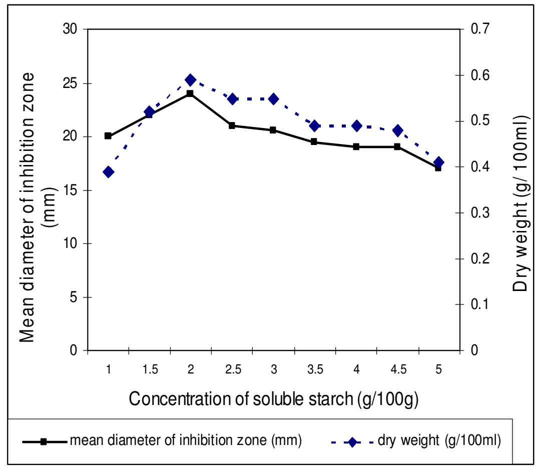
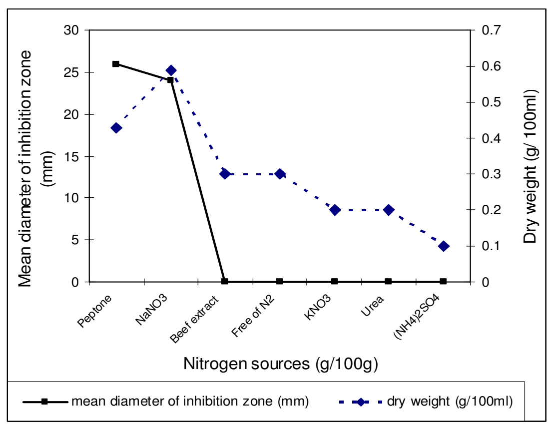


Table (6) The effect of different nitrogen sources on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*.

Nitrogen sources (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
Peptone	26	0.43
$NaNO_3$	24	0.59
Beef extract	0.00	0.30
Free of N_2	0.00	0.30
KNO_3	0.00	0.20
Urea	0.00	0.20
$(NH_4)_2SO_4$	0.00	0.10

Figure (6) The effect of different nitrogen sources on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp*.* MS-266 Dm_4 against *B. cereus*



highest productivity of MSW 2000 from *S.violatus* occurred after four days of incubation under static conditions.

Our results agreed with the findings of many researchers (Aman, 2001; Hassan *et al*., 2001; Padma *et al*., 2002; Venkateswarlu *et al*., 2004) which found that the productivity increased in shaking culture comparing with the static culture this is due to the fact that streptomycetes are obligate aerobic organisms (Holt *et al*., 1994), while AL-Zahrani (2007) found that the shaking culture reduced the productivity of *Streptomyces* J12.

Maximum yield of the active metabolite produced by *Streptomyces* sp. MS – 266 Dm4 was obtained at an incubation temperature of 30° C and this result was agreed with many researchers (Gubte and Kulkarni, 2002; AL-khaldi, 2003 and Kiviharju *et al*., 2004). Also, Hassan *et al*., (2001) studied the effect of physiological factors on the productivity of antimicrobial material produced by *S. violatus* and they found that increasing the incubation temperature from 20 to 30℃ led to increase growth and productivity of the antibiotic, while raising the temperature higher than 35℃ has had an

Table (7) The effect of different concentrations of peptone on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*.

Concentration of Peptone (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
0.03	29	0.39
0.04	30	0.40
0.05	29	0.40
0.10	26	0.40
0.15	26	0.41
0.20	26	0.43
0.25	22	0.43
0.30	21	0.43
0.35	21	0.43
0.40	17	0.43
0.45	17	0.43

Figure (7) The effect of different concentration of peptone on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

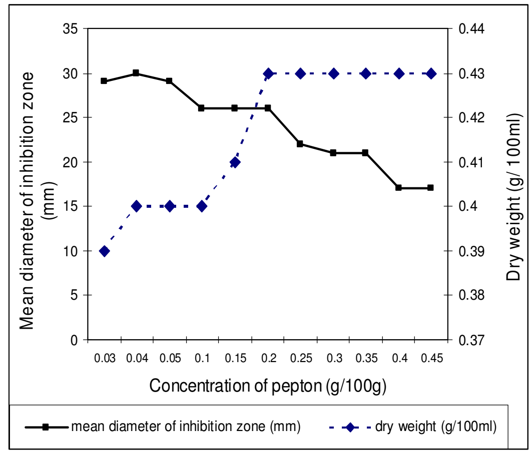
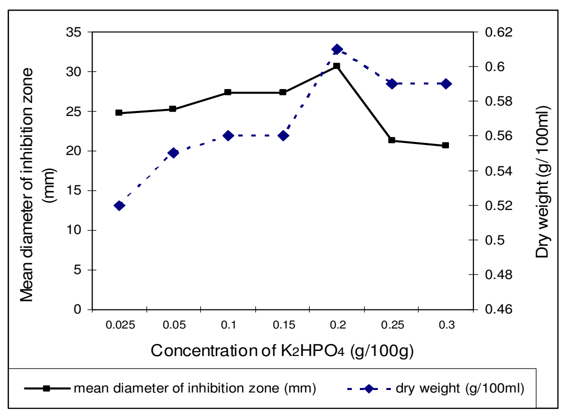


Table (8) The effect of different concentration of K_2HPO_4 on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*

Concentration of K_2HPO_4 (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
0.025	24.7	0.52
0.05	25.3	0.55
0.1	27.3	0.56
0.15	27.3	0.56
0.2	30.7	0.61
0.25	21.3	0.59
0.3	20.7	0.59

Figure (8) The effect of different concentration of K_2HPO_4 on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus.*



adverse effect on growth and productivity. Other study by Padma *et al.*, (2002) recorded that the best incubation temperature was 29℃.

In this study the maximum antibiotic activity was obtained at an initial pH 6.0. Other study by Crawford *et.al.*, (1993) recorded that the best growth of actinomycetes strains were between pH 6.5-8 and few could not grow at pH 6.0, nevertheless the failure of a large number of actinomycetes to grow at pH 5.5. EL-Naggar (1991) found that the initial pH value of the culture showed a significant influence on the maximum productivity of the antibiotic as well as on the growth of *Streptomyces nasri*. Our results are not in accordance with those obtained by Chattopadhyay and Sen (1997), who noted that pH 7.0, is the most appropriate pH values to produce the highest amount of antibiotic of different types of *Streptomyces*. On the contrary, Holtzel *et al.*, (1998) found the highest production at pH 5.5. In other research EL-Naggar *et al.*, (2003) found that the highest amount of productivity of antibiotic by *Streptomyces violatus* at pH 7.5.

Our result showed that maximum growth and antibiotic production was obtained in cultures supplemented with 2.0g /100ml soluble starch as a sole carbon source. Cultures containing sucrose, maltose or natural starch did not yield any detectable amounts of the antibiotic. Other researcher (EL-Naggar, 1991; Haque *et al.*, 1995 and Theobald *et al.*, 2000) supports this. In

Table (9) The effect of different concentration of MgSO4 on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm4 against *B. cereus.*

Concentration of $MgSO_4$ (g/100ml).	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
0.02	32	0.55
0.05	32.7	0.59
0.08	32.7	0.59
0.1	34	0.58
0.15	36	0.58
0.2	32.7	0.53

Figure (9) The effect of different concentration of MgSO4 on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm4 against *B. cereus.*

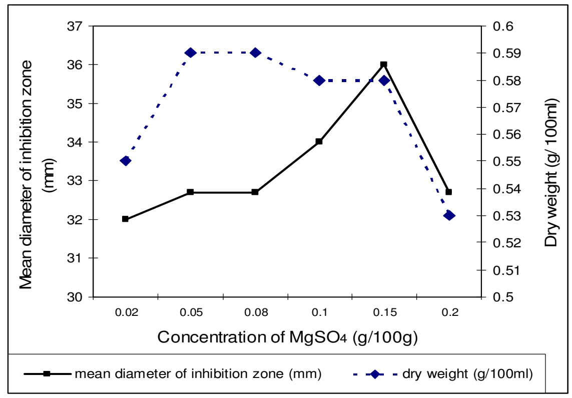
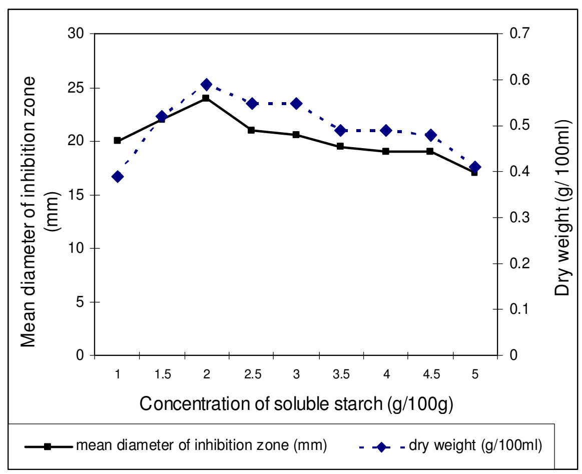


Table (10) The effect of different concentration of KCl on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*.

Concentration of Soluble Starch (g/100ml)	Mean diameter of inhibition zone (mm)	Dry Weight (g/100ml)
1.0	20	0.39
1.5	22	0.52
2.0	24	0.59
2.5	21	0.55
3.0	20.5	0.55
3.5	19.5	0.49
4.0	19	0.49
4.5	19	0.48
5.0	17	0.41

Figure (10) The effect of different concentration of KCl on the dry weight and productivity of antimicrobial agent by *Streptomyces* sp. MS-266 Dm_4 against *B. cereus*.



addition, many researchers found that starch is the best carbon source for the highest productivity of the active substance but in different concentration. Al-Khaldi (2003) found that the best concentration was 3.0g/100ml while, AL-Zahrani (2007) found that the best concentration was10gm / L. In contrast, Haque *et al*., (1995) found that glycerol was the most suitable carbon source for production *of S. antibioticus*. Gesheva *et al*., (2004) explained that there is a significant effect in the case of replacement of glucose by glycerol or lactose in the production of anti-bio-macrolide AK-111-81. Venkateswarlu *et al*., (2004) confirmed increasing the productivity of rifamycin in the presence of glucose as a source of carbon.

Among the six nitrogen sources tested, the peptone in concentration of 0.04g/l00ml was preferable to the antibiotic production whereas NaNO3 was preferable to the growth. These results are in partial agreement with (Atta, 1999). Otherwise, EL-Naggar (1991) and Aman (2001) found that sodium nitrate was the most appropriate source of nitrogen. Theobald *et al*., (2000) noted the increase in the production of antibiotic extracted from *S. antibioticus* with the presence of lysine as a source of nitrogen. Gesheva *et al*., (2004) found that the addition of ammonium succinate increase productivity of macrolide Ak-111-81. Venkateswarlu *et al*., (2004) recorded in their study that the ammonium sulphate, soybean and peanuts were the best sources of nitrogen to increase the productivity of rifamycin.

The effect of adding different concentrations of mineral salts was varied. We found that the concentration of (KCl) 0.05 g/100ml increase the productivity and dry weight which was similar to the concentration in the basic medium and consistent with the results of Aman (2001). While the concentration of (K_2HPO_4) and ($MgSO_4$) increased than in the basic medium. The results showed that there is a close relation between increased concentration of (K_2HPO_4) and ($MgSO_4$) and increase in the productivity of the active substance. Similar results were mentioned by (Ueda *et. al*., 1997; Atta, 1999 and Aman, 2001) who made it clear that the addition of different concentrations of mineral salts to the growth media of *Streptomyces* have a positive effect on growth and productivity of antibiotic. Farid *et al*., (2000) found that 0.05g / IL (K_2HPO_4) is the best concentration for the production of active substance by *Streptomyces natalensis*. Also they found that increasing the concentration of phosphate in the growth media leads to a significant increase in biomass associated with a decrease in the productivity of the active substance. El-Naggar (1991) explained that the salts of magnesium and potassium are considered the most appropriate salts for the growth of *Streptomyces*, as well as the production of active substance. The effects of magnesium availability are presumably due to requirements of this action for protein synthesis, and its depletion may restrict enzyme synthesis and activity (Aasen *et al*. 1992; Natsume *et al*. 1994).

CONCLUSION

Antibiotic productivity of *Streptomyces* isolate is inconstant, and could be increased, decreased or loses significantly under different nutritional conditions. Therefore, modified quantities and use different sources of carbon, nitrogen and mineral salts, as well as changing the growing conditions is one of the fundamentals that must be followed when studying the production of antibiotics from these organisms. The present study clearly found that there are no clear relationship between biomass and antibiotic activity.

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