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Research Article

CONTRIBUTION OF WAXES ON GRANULATION AND COMPRESSION OF NONCOMPRESSABLE DRUG:TABLETTING, DRUG RELEASE AND PHYSICO-CHEMICAL STRUCTURE

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Abstract: Tablets were pressed under constant condition from different paracetamol granules prepared using either SA or GMS (part one). The Pharmacopeal and non-Pharamcopeal tests were carried out and the results showed that it depends on the type and concentration of granulating agent used. I.R. scan showed no chemical interaction between the drug and either SA or GMS. Powder x-ray diffraction showed there is change in the crystallinety of the drug which is depending on the the type and the concentration of the granultaing agent used. The drug release indicated there is no burst effect. There was nearly complete drug release on using SA as granulating agent while the use of GMS led incomplet drug release. In every case the drug release rate is depending on the concentration of the antiaggregating agent used. The release kientics from all tablets did not follow zero oder except that from tablet prepared on using 5% GMS. The application of first order kinetics showed one phase release peroid from tablet prepared on using SA as granulating agent and two Phases peroids from tablet prepared on using GMS. The same results obtained on applying Hixsion-Crowell model. All release data from different tablets which prepared from different products followed the krosmeyer-peppes model with n value indicating that the drug release is non-Fickian mechanism. All of obtained result could be explained as a result of the mechanism of the granulating agent used. From the results and because of using much lower concentrations of either SA or GMS, it is clear the efficiencies of the preparation technique over mixing melting waxes with the drug especially the highest amount of initial drug released is only 10% from the total amount of drug in the tablet which can not considered as burst effect. It can also concluded that both granulating agents used are effective in the conversion of non-comprisable drug to comprisable one without any change in the chemical properties of the drug.

Key**words:** Paracetamol, Stearic acid , Glyceryl mono stearate, I.R., X-ray diffraction, drug release kinetics

INTRODUCTION

During the development phase, significant attention is paid to critial quality characteristics of the tablet. This phase is often characterised by use of statistical design or other means to evaluate and, where possible, quantify those formulation and frequantly process variables that significant effect on the estibilished tablet quality charactersitcs [1]. There are a number of procedures which apply specifically to tablets. Such standard in British Pharmacopoeia are: uniformity of diameter, uniformity of weight, content of active ingredient, uniformity of content, disintegration, and dissolution. In addition there are number of quality control procedures which widely applied, are not defined by the Pharmacopoeia [2]. In the literature it can be found, by all research work, an attention to qualify the prepared tablet. For example, Kumar et al[3] , prepared paracetamol tablet after wet granulation with Borassus flabellifer mucilage as a tablet binder. The auther found that the pharmacopeal and non pharmacopeal standard depends on the concentation of the binder for granulation used. Bodas et al [4], found that tablets prepared with Randia dumetorum fruit mucilage as binder showed good results and comparable dissolution profile as that of standards. The results were complied with pharmacopoeial limits.

The tablets prepared by co-processed excipient exhibited relatively higher disintegration time due to the presence of higher percentage of meltable binder. Modulation of the disintegration time was done by incorporating crospovidone [5]. Bhagwat et al [6] used GMS and SA for formulation of sustained release dosage form of verapamil. The Pharmacopeal and non pharmacopeal standards were studied and the dissolution results showed that the release of drug from matrices prepared from combination of both waxes has more retarding effect than that from GMS and SA alone. As concentration of waxes increases, release of drug from matrices decreases. The release enhancers showed that the use of lactose produces the best drug release. Dissolution of Verapamil HCl from matrices followed first order and Higuchi's square root kinetic model. Eichie et al [7] stated that the granule sizes should be controlled during tableting and/or filling into capsule in order to avoid weight and content variation while ensuring that only tablets with desirable mechanical characteristics are formed. Solanki et al [8] found that HPMC und SAPI (spherical agglomeration of paracetmol – iburofen) produces improved micromeritics and excellent tabletting with higher dissolution rate and spherical agglomeration. Reza et al [9] evaluated the comparative efficiency of different wax-lipid matrices in controlling the release of active ingredient. Carnauba wax, bees wax, glyceryl monostearate (GMS), stearic acid, cetyl alcohol and cetostearyl alcohol have been used as the hydrophobic matrices and their release-modulating were studied in terms of in-vitro dissolution testing. The results showed that proper selection of these hydrophobic materials based on their physico-chemical properties is important in

designing wax matrix tablets with desired dissolution profile.

The aim of this work is to press the granules of each produt which prepared and evaluated in the first part into tablets and evaluate the pepared tablets according to pharmacopial and non pharmacopeal standards. Also the physco-chemical propetries of each granules should be studied in correlatation to the drug relaese from each product tablet prepared using either SA or GMS as granulating agent.

MATERIALS AND METHODS

1. MATERIALS:

Acetaminophan (Sgma, USA), Stearci acid (SA) (ADWIC, Egypt), Glyceryl mon stearate (GMS)(BDH chemicals Ltd Poole, England).

2. METHODS:

2.1. I.R. Scanning:

I.R. spectra of paracetamol, SA, GMS and products prepared with different concentration of waxy substances were carried out using KBr disc and FTIR (Tensor 27 Broker, Germany) . The scanning range was from 800 cm^{-1} to 4000 cm^{-1}.

2.2. Powder x-ray diffraction analysis:

The x-ray diffraction profile of the different products were carried out using powder x-ray diffractometer (Phillips PW 1840). The measurement conditions were CuKά; filter Ni; Voltage 40kV; current 20 mA; slit 0.1 mm; scanning speed 20 mm^{-1} counts per second were related to a step scan through the peak at this speed corrected for background.

2.3. Granules compression:

The granules of each product were compressed into tabelets to evalute the ability of the different products to compression using erweke single punch machine. The tablets of each weight 300 mg was tried to prepare using a press equipped with a flat punch. All pressed tablets were prepared at constant pressure.

2.4.Characterization of the compressed tablets:

A. Uniformity of weight:

The test is carried out by taken 20 tablets form each product, weighing them individually and calculating the mean weight. The mean weight governs the permitted deviations from the means. The permitted deviation of tablet weight 250 mg or more is 5%.

B. Hardness:

The hardness of the prepared tablets was measured using Erweka hardness tester. The mean value of 5 tablets was noted in kg/cm^2.

C. Friability:

The friability of tablets of each product was measured using erweka friability tester. Tablets of known weight (W_0) are deduced in a drum for a fixed time and fixed rpm and then weight again (W). The percentage of friability was calculated from the loss in weight following formula:

$$\text{Friability \%} = [(W_0 - W) / W_0] \times 100$$

D. Disintegration of tablets:

The test was carried out using erwika disintegration tester. A sample of six tablets, placing one in each tube and agitating the tube in a water path at 37℃± 0.5. The time in which no residue of the tablet fragment remains in the tube or completely dissolved was noted as a disintegration time.

E. Dissolution rate study:

The dissolution rate of paracetamol from tablets of different formulations was studies using USP 22 dissolution apparatus. The dissolution media was 900 ml of 0.1 N hydrochloric acid heated 37 °± 0.5 and rotated at 50 rpm. 5 ml samples were withdrawn periodically over the dissolution time of 2 hours and assayed spectrophotometrically at 243 nm. After each sampling equal volume of fresh media solution with the same temperature was replaced. All experiment was carried out in triplicate.

F. Kinetics of drug release:

To determine the value of the regression coefficient (r^2) and mechanism of drug release form different formulations, the cumulative release data were fitted to different models. The models applied were zero-order (Cumulative percentage drug released v/s time), first-order (log cumulative percentage drug retained v/s time), Higuchi's square root of time (Cumulative percentage drug released v/s square root of time) and Korsemeyer-peppas double log plot (log of fraction of drug released v/s log time) and Hixson-Crowell cube root law (cube root of drug % remaining in matrix vs. time).

$$M_t = M_0 + k_0 \quad (1)$$

$$\text{Log } M_t = \text{Log } M_0 + k_1 t \quad (2)$$

$$M_t = M_0 + k_H t^{1/2} \quad (3)$$

$$M_t / M_0 = k t^n \quad (4)$$

$$M_0^{1/3} - M_t^{1/3} = K_{HC} t \quad (5)$$

Where M_t is the cumulative amount of drug released at any time, t and M_0 is the dose of the drug incorporated in the delivery system. k_0, k_1, k_H and K_{HC} are rate constants for zero-order, first order, Higuchi models and Hixson-Crowell Cub Root equation, respectively.

RESULTS AND DISCUSSION

It was tried to press the products prepared by using different concentrations of either SA or GMS without any additives to improve the flow character of the products, as a pure comparison study. The pure drug could not press into tablet. On using 5% SA, nearly 50% of the prepared tablets were capped and stained the hand with the powder of drug. These observations were markedly decreased on using 10% SA and completely disappeared on using 15% SA as a granulating agent. These effects would not observe on using different concentrations of GMS.

Standards in British Pharmacopoeia for tablets are: uniformity of diameter, uniformity of weight, content of active ingredient, uniformity of content, disintegration, and dissolution. Uniformity of diameter should be considered if the tablets containing the same amount of drug but made by different manufacturers differ greatly in size [2] which will not consider in this comparison study.

Content of active ingredient and uniformity of content, which depend on the tablet weight and amount of additives, will not also be considered because of low concentration of additive and high concentration of drug used. In addition they should be considered on large scale study or on trying to improve the flow property of the products by admixing with excipient(s) prior to tableting or encapsulation [10].

The results of the Pharmacopoeial and non Pharmacopoeial tests are summarized in tables (1, 2). A tablet is designed to contain a specific amount of drug in specific amount of tablet formula. The United States Pharmacopeia allows the use of a weight variation test as a measure of uniformity of dosage unites provided the tablet being tested contains 50 mg or more [11]. From table (1) it can be noticed that the mean tablet weight in case of using 5% SA is away from the permit deviation which will be within the permit deviation on using higher concentrations of SA. At the same time, for all products prepared on using different concentrations of GMS, from table (2) it can be observed that the mean tablet weight is completely away from the permit deviation.

Table 1: ***Physical parameters for different tablets prepared using SA:***

SA concentration %	5%	10%	15%	20%
Weight variation	274.7	290.8	294.2	295.105
±SD	12.676	6.631	9.10	6.599
Hardness	0.3	0.3	0.3	0.3
Friability %	24.943	16.878	9.897	8.418
Disintigration time (min)	31,50	16,75	14,75	14,5
±SD	5,448	1,707	3,5	1,732

Table 2: Physical parameters for different tablets prepared using GMS:

GMS concentration %	5%	10%	15%	20%
Weight variation	276.95	278.088	279.825	280.433
±SD	0.013	0.007	0.005	0.002
Hardness	0.5	4.025	3.625	1.582
Friability %	15.143	1.452	0.385	0.164
Disintigration time (min)	80,00	88	50	35
±SD	3.999	2.886	3.301	1.881

Aulton [11] reported that, failure to comply with the standard (uniformity of weight) may be due to uneven feeding of granules into the die or irregular movement of the lower punch, producing a die space of every capacity. Liebermann et al [12] also stated that if everything working well mechanically, the weight can be caused to vary by poorly flowing granulation, which causes spasmodic filling of the dies. Mady [13] was found that all products have low flow property and the products prepared on using SA formed irregular granules with increasing SA concentrations. This is may explain the finding stated before about the weight variation on using SA. At the same time, all products prepared by using GMS were spherical with better flow than that prepared on using SA but also have higher bulk density by which the die will be filled during the compression process. This may explain the deviation of mean tablet weight from the standard in case of using GMS especially it can be noticed that all tablets are pressed without the addition of glidant. From above it would be advice to control the tablet weight for each patch before tableting when different formula used which did not occur in this comparison study to avoid the change in the tableting compression force.

Hardness for all tablets prepared from granules using different concentration of SA is the same (table 1) while that for tablets prepared from granules using different concentrations of GMS is increased from using 5% GMS to 10% GMS and then deceased (Table 2). The friability % for all tablets prepared from granules using different concentration of SA is decreased with increasing the concentration of SA used. There is a liner relationship between the concentration of SA used and the decreasing of the friability %. At the same time from table (2) it is obvious that the friability % is markedly decreased in case of using 10% GMS than that in case of using 5% and then decreased to become nearly zero on using 20% GMS.

Tablet disintegration test for all products was also carried out for determination of the designation time. It was noticed that, tablets prepared by using different concentrations of SA would be split into particles, passed from the basket and then dissolved while that prepared on using GMS dissolved slowly with decrease in size till completely disappeared. The disintegration time of tablets prepared on using different concentration of SA is markedly decrease from tablet

prepared on using 10% than that 5% and then become nearly the same. Reza et all [9] stated that the free carboxylic acid group of stearic acid enhance the formation of hydrogen bonding with surrounding dissolution medium and facilitated wetting of matrix. Also the molecular length and cross sectional area of stearic acid is 25 A˚ and 22 A˚ respectively. The high molecular dimension of stearic acid also contributed to enhanced formation of hydrogen bond with the surrounding medium. Increase SA concentration leads to increase the wettability of the matrix resulting decrease the disintegration time. The disintegration time of tablet prepared on using GMS can be arranged in the following order from 10% > 5% >15% > 20% GMS used. That is may be due to the surface active property of GMS [14] and its mechanism as granulating agent.

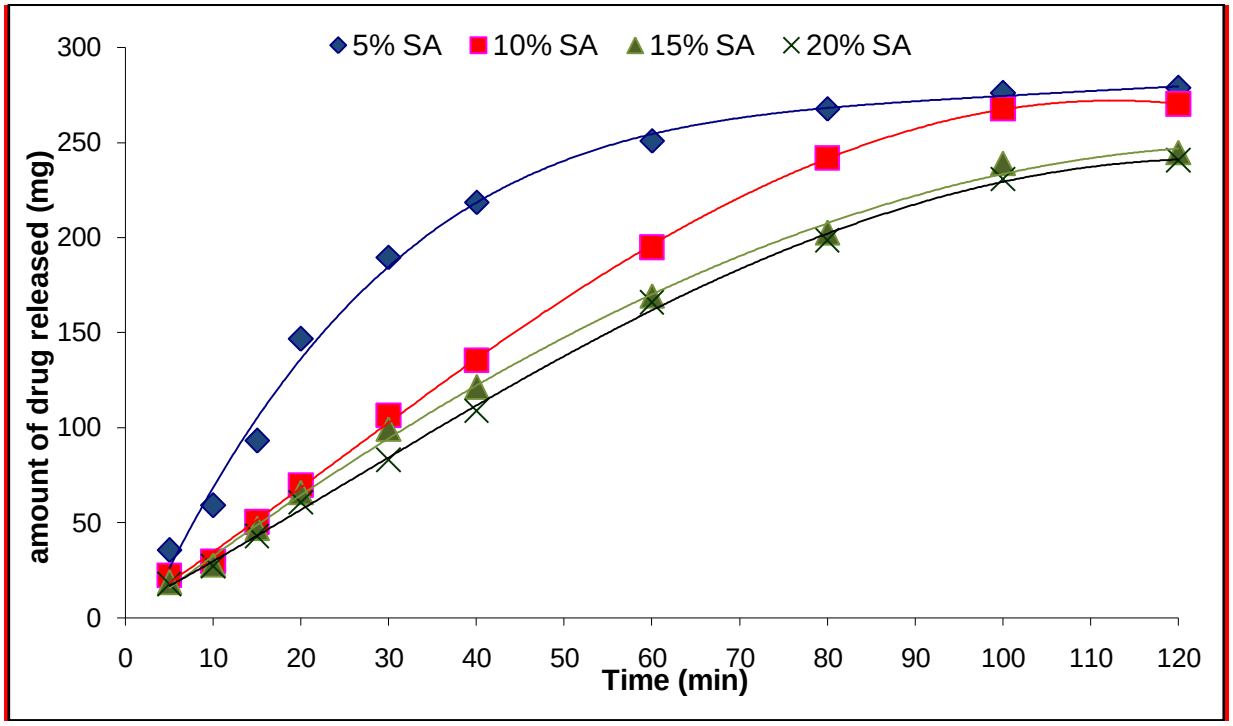


Figure (1): Dissolution of drug from tablet prepared on using SA for granulation:

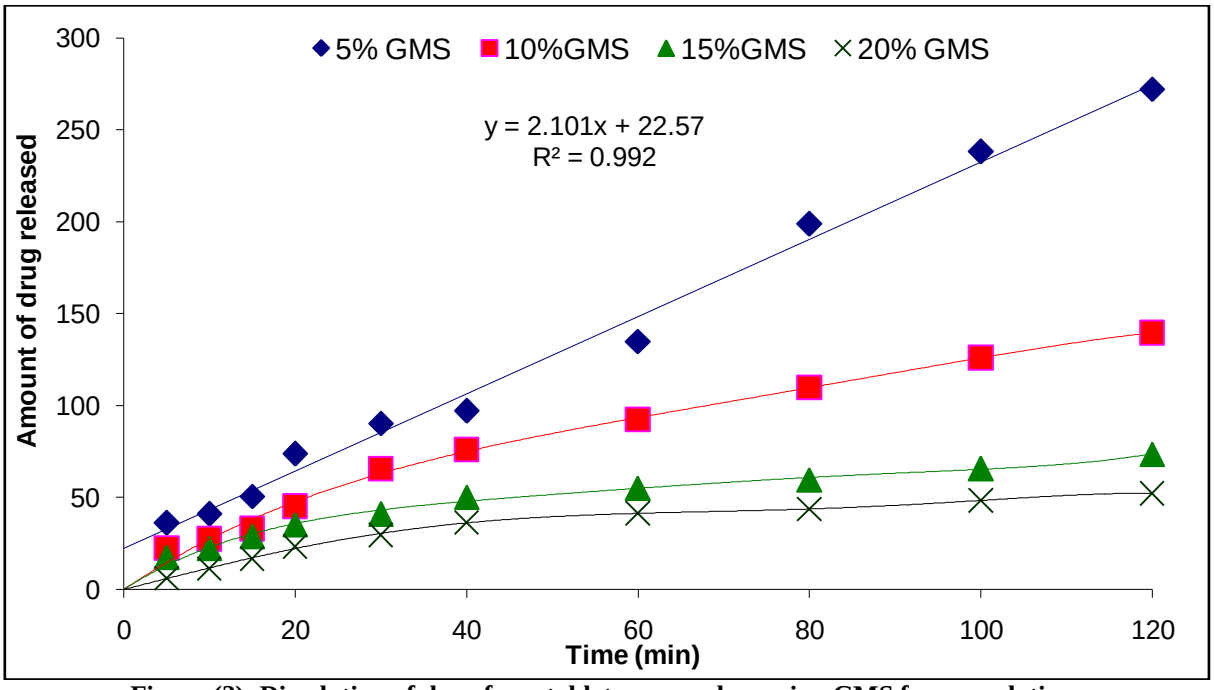


Figure (2): Dissolution of drug from tablet prepared on using GMS for granulation:

The drug release from different tablets prepared using different concentrations of either SA or GMS was studied Figures (1, 2). From the figures, it can be noticed that in every case there is amount of drug released after 5 min which represent the amount of free drug on the surface of the tablet. This amount decreased with increase the

concentration of either SA or GMS [9]. It was also found that there is a liner relationship between the amount of initial drug released and the concentration of GMS used. This linear relationship was not found in case of using different concentrations of SA. From figure (1) it can be observed that there is a complete drug release from the tablets prepared on using different concentrations of SA. On contrary, there is incomplete drug release in case of using GMS which is markedly decreased with increase the concentration of GMS used (figure 2). Also in every case, the amount of drug released after 2 hours dissolution time on using 5% > 10% > 15% > 20% of all products prepared on using of either SA or GMS [6]. It is also important here to report that, plotting of drug release percent against time did not change any release profile stated before except that in case of using 15 and 20% SA. These two profiles look to some extend overlapped. The drug release results led to trying to study the physico - chemical structure of the granules prepared by using different concentrations of either SA or GMS.

IR scan for paracetamol and all products prepared on using different concentrations of SA was carried out figure (3). IR scan of paracetamol showed that the N-H amide stretch band can be seen quite clear at 3326 cm^{-1} although it is in the top of the broad OH stretch. A very broad band at 3162 cm^{-1} is due to phenolic OH stretch. A non clear band at 2880 cm^{-1} is due to underlying of OH absorption as a result of C-H stretching. The stretching of C=O amide at 1654cm^{-1} occurs at a low wave number. The aromatic C=C stretching at 1610 cm^{-1} is a strong band because the aromatic ring has polar substituent's which increase the dipole moment of the C=C bonds in the ring. Also an evidence of doublet at 1506 cm^{-1} from aromatic C=C stretch as a result of the interaction the aromatic ring with the substituent's . The second amide stretching band is at 1557cm^{-1} while that at 1247cm^{-1} is due to C-N-H group. The peak at 839cm^{-1} may be due the para-disubstituted aromatic ring. IR scan for all products prepared on using different concentrations of SA indicated there is no change of all drug characteristic peaks. Accordingly it can be concluded that there is no chemical interaction between paracetamol and SA of all concentrations used.

Studying the IR scan of all products prepared in the presence of different concentrations of GMS, it can recognize all characteristic peaks of the drug of all GMS concentrations used (figure 4). This result indicates, there is no chemical interaction between the drug and GMS. In addition there are two peaks at 1720 cm^{-1} and 2851 cm^{-1} which are due to the carbonyl ester and C-H vibration of GMS. The intensity of these two peaks increased with increase the concentration of GMS used.

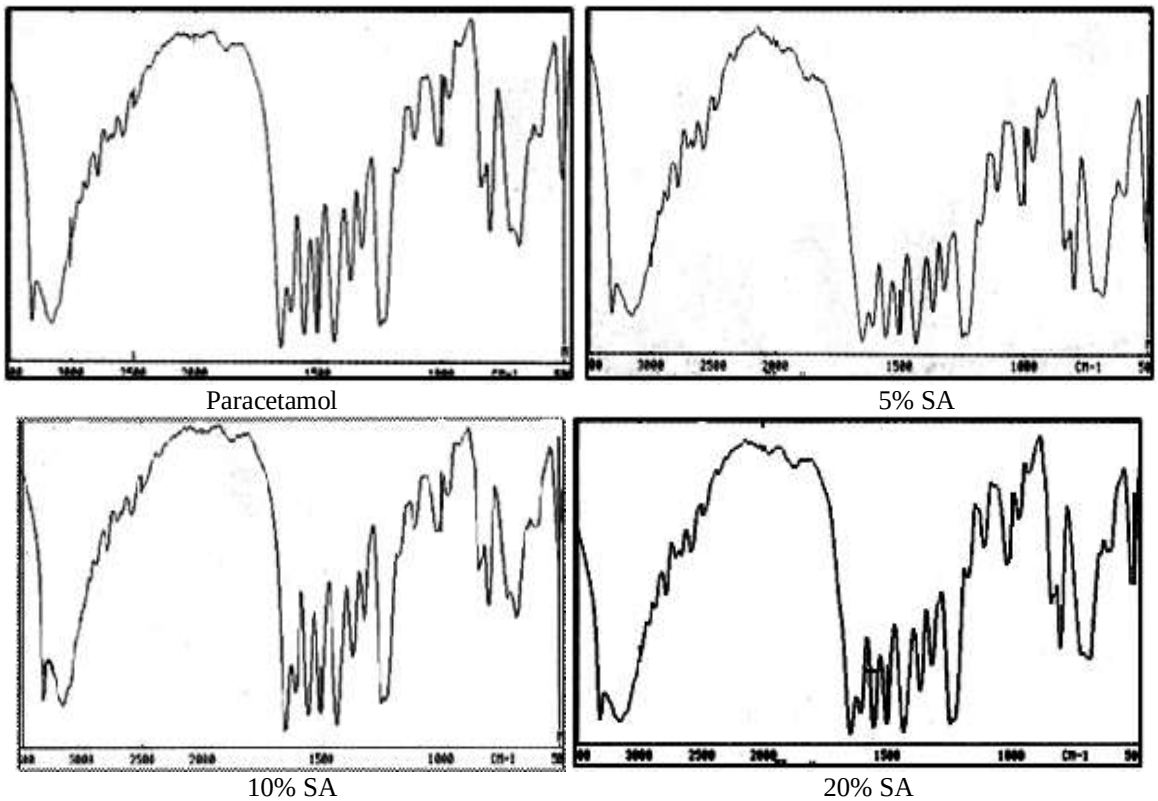


Figure (4): IR scan for products prepared on using GMS as granulating agent:

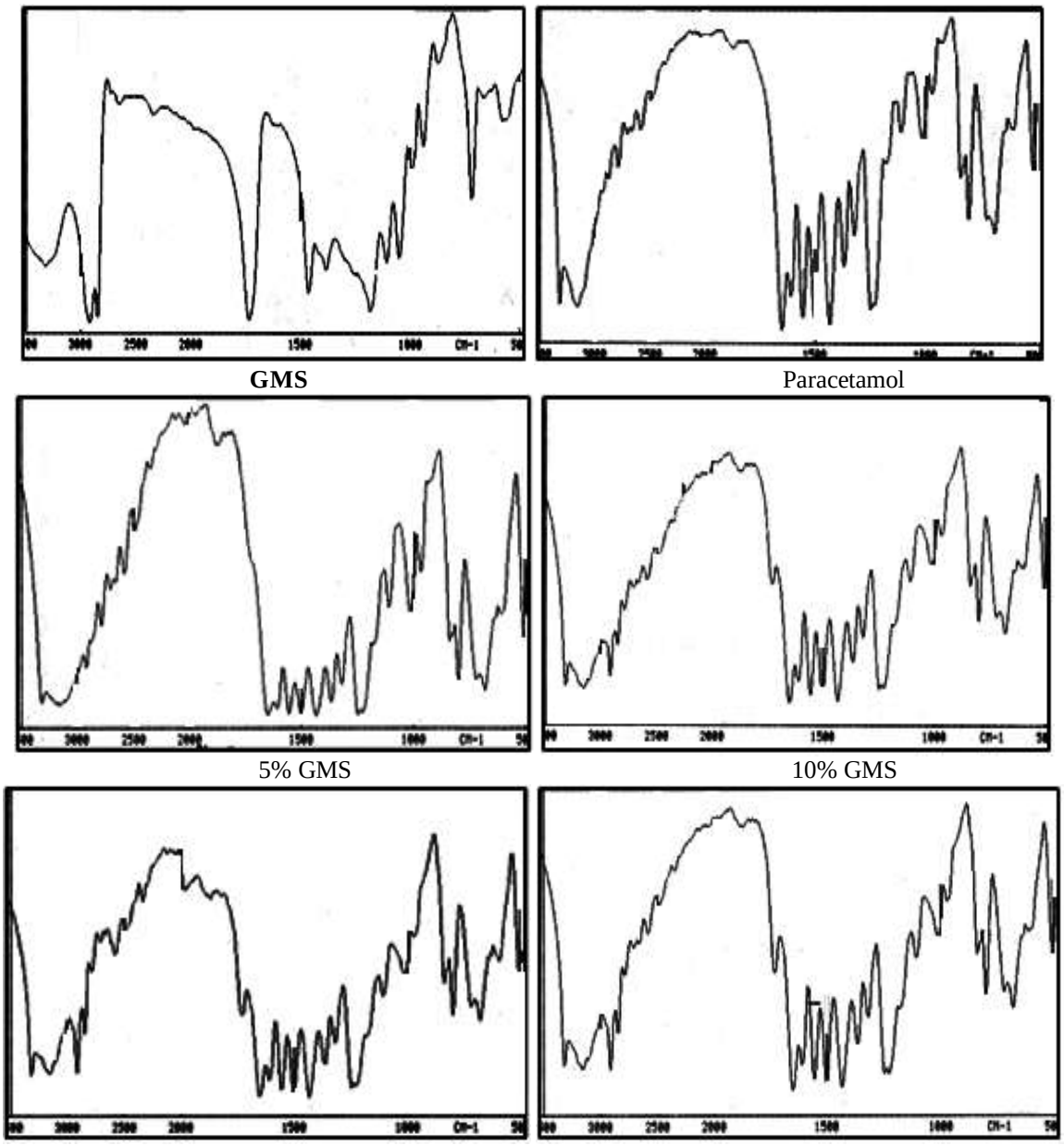


Figure (3): IR scan for products prepared on using SA as granulating agent:

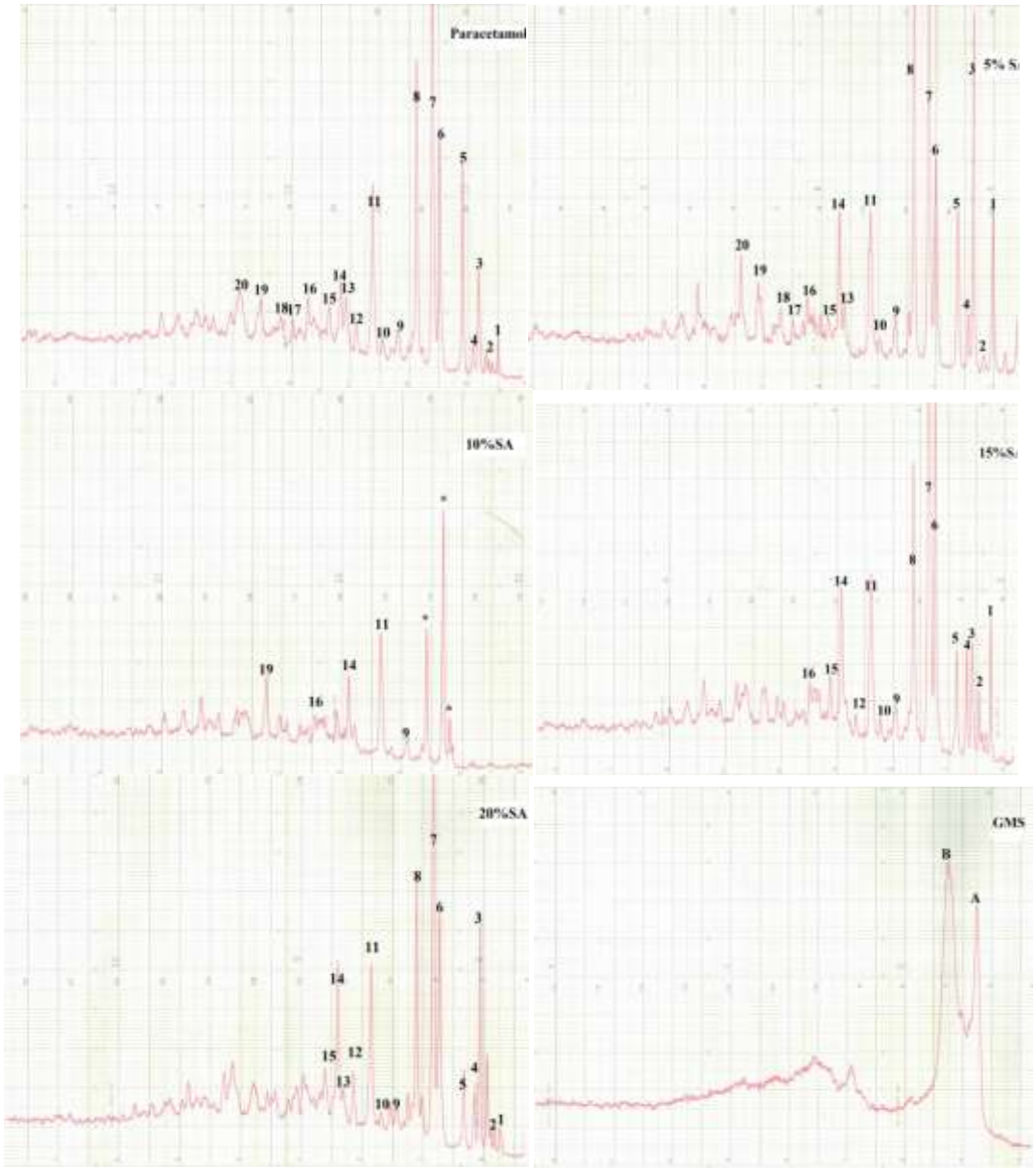
To study the effect of the granulating agents on the crystallinety of the drug, powder x-ray diffraction for all products was carried out (figure 5). The characteristic peaks for the drug were recognized by Arabic numbers. In case of using 5% SA it can be noticed that, there are an extreme increase in the intensity of peaks number (1, 3, 7, 8, 14, 20). The peak number 12 is disappeared. But on using 10% SA, all characteristic peaks of the drug are disappeared except numbers (9, 11, 14, 16, 19) and appearance of new peaks signed with (*).

At the same time the use of 15% SA led to the reappearance of all drug characteristic peaks with an increase in the intensity of peaks numbers (1, 2, 4, 14) and decrease the intensity of peak number (5). The same effect can be also observed on using 20 % SA with decrease the intensity of peak number (1) and increase the intensity of peak number (14). When GMS used as granulating agent it can be noticed that the use of 5% GMS led to increase the intensity of all drug characteristic peaks and the appearance of new peak signed with (*). This effect is more pronounced on using 10% GMS. But in case of using 15% GMS the intensity of peaks numbers (1, 3, 20) is increased but for numbers (5, 6, 7, 9) is decreased. This effect is more pronounced on using 20% GMS. In addition GMS shows two peaks signed with (A, B) and both are completely disappeared by all products prepared on using GMS as granulating agent.

Villiers et al [15] found that the precipitation of acetaminophen in the presence of PVP decreased the degree of crystallinety of acetaminophen only when both were in solution (ethanol) or partially dissolved (water at 10°C). In cold water, the decrease in crystallinety was less because the solubility of acetaminophen was less. The decrease in the amount of

crystalline material was the result of the formation of a glass-like, X-ray amorphous solid solution. The formation of this glass-like amorphous material could be followed by XRD analysis of powdered samples. Ford et al [16] stated that, the X-ray powder diffraction spectra of untreated paracetamol and samples crystallized from media containing 0.5% w/v of different grades of PVP exhibited essentially similar diffraction patterns, suggesting that particles crystallized in the presence of PVP did not undergo structural modifications. However, the differences in the relative intensities of their peaks may be attributed to differences in the crystal sizes and habits of the samples [17,18]. Mady [13] studied the mechanism by which the granules formed on using either SA or GMS and its effect on the granules surface and shape. It was found that the presence of either SA or GMS led to change the drug crystal agglomeration which is more pronounced on using higher concentrations. The effect of GMS was markedly higher than that of SA. In addition it cannot ignore the solubility of paracetamol crystal in the melted waxy base and its effect on the recrystallinety of the drug after cooling.

From the above, it can be concluded that, the mixing of either SA or GMS in powder form with the drug, elevating the powder temperature with stirring above the melting point of the granulating agent, led to change the crystallinety of the drug without any chemical structure changes which will be reflected on the granules characters [13] and also the Pharmacopeial and non-Pharamcopieal characters of the prepared tablets stated before.



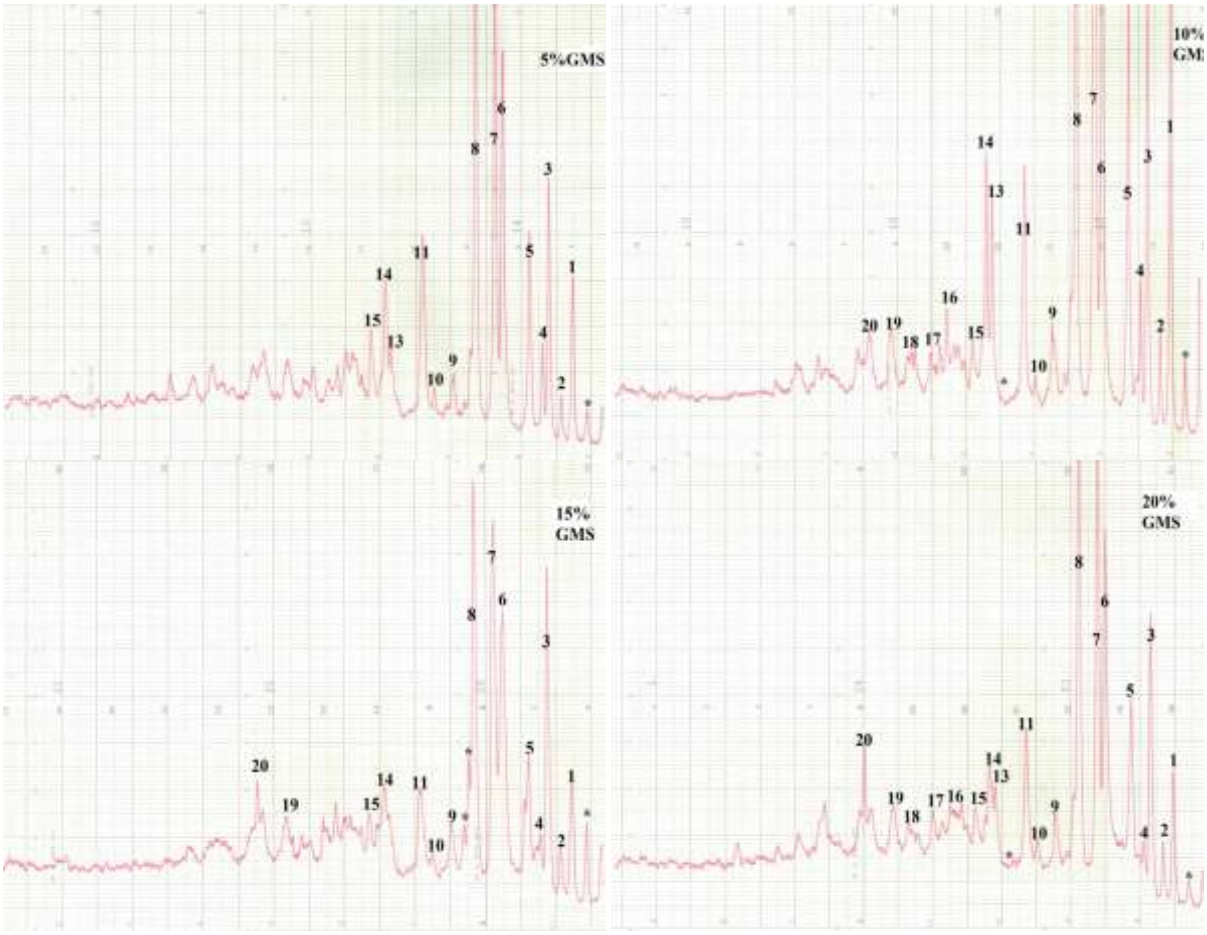


Figure (5): X-ray diffraction of all granules prepared by either SA or GMS:

Kinetic approach of drug release from different products tablet:

To compare the dissolution profiles between all products, different models dependent (curve fitting) are used. From figures (1,2), it can be noticed that the drug release rate from all tablets did not follow zero order kinetics except that prepared from granules using 5% GMS with r^2 value of 0.992 and intercept equal 22.576. The value of intercept represents the amount of drug on the tablet surface and 13.713 mg (the difference between the amount measured after 5 min dissolution and the tablet surface drug) needs 5 min to be released. The zero order kinetic data for other products would not considered for two reasons. First, the r^2 values are lower than 0.965. Second, the intercept values are higher than the amount of drug released after 5 min.

Table (3): Drug release kinetics from tablets prepared on using different concentrations of SA for granulation:

		First order			Higuchi			Pppas	
	r^2	$K_1(h^{-1})$	intercept	r^2	$k_H(h^{-1/2})$	intercept	r^2	n value	$K_{kp}(h)^{-n}$
5% SA	0.9958	-0.0158	2.0274	0.9776	16.926	-28.649	0.9822	0.6534	0.3839
10% SA	0.9747	-0.0111	2.0788	0.9826	12.716	-27.786	0.9811	0.6191	0.2005
15% SA	0.9928	-0.0088	2.0396	0.9911	11.344	-23.011	0.9887	0.6233	0.1757
20% SA	0.9861	-0.0087	2.0436	0.9802	11.77	-25.470	0.9926	0.6150	0.1818

From Table (3), it can be noticed that, the drug release profile from all products tablets prepared on using different concentrations of SA is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish (First order kinetics). The rate of drug released is depending on the concentration of SA used with nearly equal intercept indicating the symmetry of the effect of SA concentration on drug released. On contrary from figure (6) it can be noticed that, the release of the drug from the product prepared on using

5% GMS, follows first order kinetics with two-phase release process [19] and a 30 minutes transition stat between the two phases (Table 4). The second phase has high dissolution rate constant. Normally these results should not be considered because of low r^2 value. But it was taken to compare with what would occur on using other GMS concentrations.

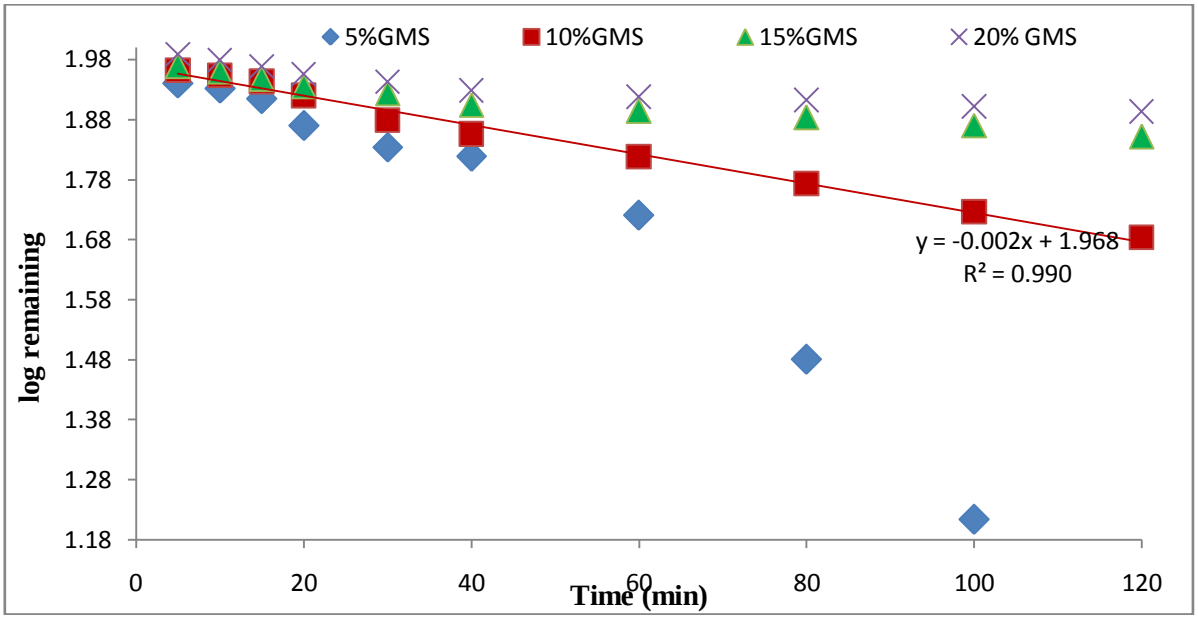


Figure (6): First order plotting of drug release from tablet prepared on using different concentrations of GMS:

Table (4): First order drug release kinetics from tablets prepared on using different concentrations of GMS for granulation:

	Phase time min	r^2	$K_1(h^{-1})$	intercept	Phase time min	r^2	$K_1(h^{-1})$	intercept
5% GMS	**5-30**	0.9565	-0.0046	1.9718	**60-120**	0.953	-0.0174	2.8298
10%GMS	**5-120**	r^2	0.9907	$K_1(h^{-1})$	-0.0024	intercept	1.9683	
15%G MS	**5-40**	0.9852	-0.0017	1.9951	**60-120**	0.990	-0.0004	1.9450
20% GMS	**5-40**	0.9879	-0.0018	1.9763	**60-120**	0.982	-0.0006	1.9325

The release rate from tablet prepared on using 10% GMS, shows only one phase. At the same time the release form tablets prepared on using 15% and 20% GMS shows again two release phases without together release change point according to the correlation coefficient (r^2) data. Also the value of release rate constant of the second phase is very low comparing with that in case of 5% GMS. Since in case of first order release model, the release rate is proportional to the residual drug activity of the drug in the reservoir [18] and from the results of application of first order release kinetic on the release data from tablets prepared on using different concentrations of GMS, it can be concluded that, the use of 10% GMS has a transition physical drug entrapment stat which would be reflected on the drug release. That is, maybe, due to the physico-chemical properties of GMS and its granulation mechanism [13]. This result is also in agreement with the result of x-ray diffraction analysis stated before.

Treating the release data according to Higuchi model equation for all products, yielded a fairly good linearity confirming that the release permeation data followed the Higuchi model with negative values on the time axis indicating the presence of initial drug release. The Higuchi rate constant and the intercept values from products prepared on using SA is very high (Table 3) indicating greeting extraction of the drug from the vicinity of the matrix surface [9]. This finding can be only noticed on using 5% GMS (table 5). These findings support the suggested difference agglomeration mechanism between the using of SA or GMS and also in agreement with what stated about the role of GMS on coalescence step [13].

Table (5): kinetics release data of products prepared on using GMS:

	Higuchi			Krosmayer-peppes		
	r^2	$k_H(h^{-1/2})$	intercept	r^2	k	n-value
5% GMS	0.9557	9.7358	-18.212	0.9510	0.5924	0.6749
10% GMS	0.9931	5.2006	- 5.4927	0.9827	0.4332	0.6181
15% GMS	0.9833	2.4635	+2.1135	0.9882	0.5271	0.4526
20% GMS	0.9614	2.1949	-0.9593	0.9502	0.0491	0.6553

From the above and because of using much lower concentrations of either SA or GMS, it is clear the efficiencies of the preparation technique over mixing melting waxes with the drug especially the highest amount of initial drug released is only 10% from the total amount of drug in the tablet which can not considered as burst effect.

On fitting the release data for all products according to the exponential equation, from tables (3, 5) it can be noticed that the value of r^2 is high enough to evaluate the release data according to the exponential equation. The value of n of the products prepared on using different concentrations of SA is nearly the mean of the two limits values [20] which indicating the release follows non-Fickian (Anomalous) release (diffusion and dissolution). This expected release mechanism could be explained according to the solubility of the drug in the dissolution media and its diffusion through the matrix as result of the using of stearic acid [9]. In case of using GMS, from table (5), it can be concluded that the release mechanism on using 5% and 10% GMS follows non-fickian mechanism (diffusion-dissolution). But in case of 15% GMS it is pure diffusion mechanism which will be again non-Fickian on using 20% GMS. This disturbance in the release mechanism may be due to the mechanism by which GMS act as granulating agent [13] and also its property as a surface active agent [9].

From above, it is assumed that the release rate is limited by drug particles dissolution rate, by the diffusion that might occur through the polymeric matrix and also due to drug solubility in the dissolution medium. Accordingly, Hixson-Crowell model was also applied for all release data. According to r^2 value from table (6), it can concluded that, although the release kinetics from all tablets prepared on using SA follows first order kinetics with one release phase, Hixson-Crowell model shows two phase release periods. The first phase period is nearly the same but the second phase is depending on the concentration of SA used, indicating the retarding effect depend on the concentration of SA used. There is no correlation between the rest dissolution time (till 120 min) and drug release. The release rate for the same release period in both phases depends on the SA concentration used. Also concerning with the release period and rate 10% SA used, looks out from the order.
The first release period in case of using 5% and 10% GMS are the same while that 15 and 20% have shorter period (Table 7). But in every case the second release phase have the same release period which may be due to incomplete drug release. Also the dissolution rate depends on the concentration of GMS used. Concerning with the release period and rate of 10% GMS used looks out from the order.

Table (6): Hixson-Crowell model for release data from tablets prepared on using different concentrations of SA for granulation:

	Phase time min	r^2	K	intercept	Phase time min	r^2	k	intercept
5% SA	5-20	0.9979	0.0931	1.8310	30-60	0.9659	0.0127	3.6972
10% SA	5-30	0.9851	0.0574	1.7315	30-60	0.9854	0.0196	2.9288
15%SA	5-20	0.9944	0.0693	1.5757	30-100	0.9788	0.0164	2.966
20%SA	5-20	0.9983	0.0669	1.5720	30-120	0.9551	0.0188	2.8084

Table (7): Hixson-Crowell model for release data from tablets prepared on using different concentrations of GMS for granulation:

	Phase time min	r^2	K	intercept	Phase time min	r^2	k	intercept
5% GMS	5-30	0.9574	0.0358	2.1288	40-120	0.9725	0.017	2.6214
10% GM	5-30	0.9913	0.0086	2.7242	40-120	0.9877	0.0092	2.6695
15%GMS	5-20	0.9995	0.0335	1.7373	40-120	0.9941	0.0043	2.5156
20%GMS	5-20	0.9933	0.0509	1.1366	40-120	0.989	0.0038	2.3351

Accordingly from the results of application of Hixson-Crowell model and the value of n from the application of Kroysmayer-peppes model, it can be concluded that, there are 2 factors controlled the drug released from the tablet prepared from all products which are: dissolution rate of the drug and the granulating agent used. The use of GMS led to more control of drug release than that in case of using SA. Also the use of GMS led to incomplete drug release. That is due to the mechanism by which GMS act as granulating agent and the coalescence of the agglomerated particles while SA act only by agglomeration of the drug particles on the surface of its particle.

Conclusion:

From this study it can concluded that both granulating agents used are effective in the conversion of non-comprisable drug to comprisable one without any change in the chemical properties of the drug. The drug release from the tablets has not rapid initial drug release which has negative effect on the therapeutic effect of the drug. GMS has more controlling effect than SA and also has incomplete drug release which is due to the mechanism by which each acts as granulating agent. The use of lower concentration of GMS produce product which has nearly complete drug release. Because of using much lower concentrations of either SA or GMS, it is clear the efficiencies of the used granules preparation technique over mixing melting waxes with the drug especially the highest amount of initial drug released is only 10% from the total amount of drug in the tablet which cannot as considered as burst effect.

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