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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF AMOXICILLIN TRIHYDRATE USING SYNTHETIC SUPERDISINTEGRANTS

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ABSTRACT

In present study, the fast dissolving tablets of Amoxicillin Trihydrate were prepared by direct compression technique using microcrystalline cellulose (MCC) as direct compressible diluents. Sodium starch glycolate (SSG) and croscarmillose sodium (CCS) used as synthetic superdisintegrants. The swelling indices of the superdisintegrants were also compared. Among both the superdisintegrants, croscarmillose sodium showed the highest swelling index. The blends showed satisfactory flow properties. Eight formulations were prepared using different concentrations of Superdisintegrants and were investigated for their effect on the disintegration time and dissolution rate of the tablets. Tablets were also evaluated for weight variation, hardness, thickness, friability and drug content. All the tablets exhibited acceptable pharmaco-technical properties. Tablets prepared with the blend of CCS (60mg) exhibited quicker disintegration. According to the present study, it was found that tablets of batch F8 (blend containing CCS 60mg) showed better disintegrating property as well as % drug release (99.78% within 25 min.) than the most widely used synthetic superdisintegrants like SSG in the formulations of FDTs.

KEY WORDS: Orodispersible tablets, Mouth dissolving tablets, Amoxicillin Trihydrate, SSG, Croscarmellose sodium.

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INTRODUCTION

Fast dissolving tablets (FDTs) have received ever-increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry[1] .Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. These dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva. They release the drug as soon as they come in contact with the saliva, thus obviating the need for water during administration[2]. Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms[3].Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[4].Therefore for the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result the demand for developing new technologies has been increasing enormously. Since the development cost of a new drug molecule has been very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency[5].To fulfill the medical needs and to overcome these drawbacks, fast dissolving tablets (FDTs) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds[6]. Antibiotics are prescribed by doctors for the treatment of mild to moderate infection which should be taken for a minimum time interval of 3-5 days. Some patients e.g hectic community, travelled community are not able to take the complete course due to some reasons .So fast dissolving tablet of antibiotics are very acceptable dosage form which are helpful to recover the patient from a infectious disease. Amoxicillin Trihydrate, a beta-lactum antibiotic, was selected as the model drug as it was widely used as a first line treatment of mild to moderate infection of ENT (ear, nose and throat), respiratory tract, skin and genitor-urinary tract. Amoxicillin is 80% absorbed by oral route with good efficacy, safety and limited adverse effect. The objective of the study was to choose the best superdisintegrant by comparative evaluation which gives a FDT of least disintegration time and good drug release profile.

MATERIALS AND METHODS

Amoxicillin Trihydrate was procured from commercial market. MCC, croscarmellose sodium, Aerosil were purchased from S.D Fine Chemicals Ltd., Mumbai. SSG, sodium saccharin and magnesium stearate were obtained from chemical store, Department of pharmaceutical sciences Kurukshetra University Kurukshetra.

Preparation of blends and tablets

Different formulations (F1 to F8) were prepared by direct compression technique (table-1). All the ingredients were weighed as specified in the formula (table-1). Drug diluents, lubricant and Disintegrant were passed through sieve # 80. The drug was first mixed homogeneously with diluents and Disintegrant in a mortar and pestle and required degree of fineness was attained.

Finally aerosol and magnesium stearate were added and mixed. The resultant blends after micromiritic evaluation, were directly compressed using 13mm flate punches with tablet weight 600 mg in a multipunch rotatory machine. A batch size of 50 tablets was prepared in each formulation.

Table 1
Formulation of Amoxicillin Trihydrate tablets containing different concentration of superdisintegrants

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	250	250	250	250	250	250	250	250
SSG	15	30	45	60	-	-	-	-
CCS	-	-	-	-	15	30	45	60
MCC	317	302	287	272	317	302	287	272
Mg.stearate	12	12	12	12	12	12	12	12
Aerosil	3	3	3	3	3	3	3	3
Sod.Saccharin	3	3	3	3	3	3	3	3
Total wt. (mg)	600	600	600	600	600	600	600	600

Swelling index

According to B.P Swelling index is the volume in milliliters that is occupied by 1gm of drug or plant material after it has swallon in an aqueous liquid for 4hr. The swelling index of SSG and CCS were calculated according to BP specification. The swelling index study was carried out in 3 liquid like water, 0.1 N HCL and phosphate buffer 6.8. Sweeling index which represent the volume in mL occupied by the swelling of 1 gm plant material, under specified conditions. Swelling index value of both Superdisintegrants *viz.* CCS and SSG were determined. For this an accurately weighed 1 gm of the disintegrant under study was transferred into 25 mL glass Stoppered measuring cylinder. To this 25 mL of water was added and the mixture was shaken thoroughly after every 10 min for 1 hr. It was then allowed to stand for 3 hr at room temperature, and the volume in mL occupied by the Superdisintegrants was measured[7].

Evaluation of blends

The quality of tablets is generally dictated by the quality of physiochemical properties of the blends. The flow property of blends was determined by calculating angle of repose by using funnel method. Compressibility index and hausner ratio were also determined by using bulk density and tapped density.

Angle of repose

Flow properties of the blend were evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing core method of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its top a given height (1 cm), h, above graph paper placed on a flat horizontal surface. The powder was carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, with r being the radius of the

base of the blend conical pile and the angle of repose (θ) was calculated by using the eqn.1[8]
Tan θ = h/r **… (1)**

Bulk density and Tapped density
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by using tap density tester. A suitable amount of granules from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 100mL measuring cylinder. After observing its initial volume, the cylinder was allowed to tap on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula.
LBD = weight of the powder / volume of the packing **… (2)**
TBD = weight of the powder / tapped volume of the packing **… (3)**

Compressibility index
Compressibility index of the powder was determined by Carr's compressibility index as given by following eqn.[9]
Carr's index (%) = [(TBD – LBD) x 100]/TBD **… (4)**

Hausner ratio
It is the ratio of tapped to loose bulk density was calculated by using the following eqn.
Hausner ratio = TBD)/ LBD **… (5)**

Evaluation of fast dissolving tablet of amoxicillin trihydrate tablets
The prepared tablets were evaluated as per standard procedure for weight variation, thickness (vernier caliper), hardness (Pfizer hardness tester) and friability (Roche friabilator), drug content and disintegration time.

Tablet hardness
Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. The hardness of prepared tablets was determined for 10 tablets of each batch by using Pfizer tablet hardness tester.

Friability
Friability test was done with the help of Roche friabilator. Six tablets were weighed and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes. The tablets were reweighed after removal of the fine particles using 60 no. mesh. The percentage friability was calculated by using the formula:
% friability = (Loss in weight/ Initial weight) ×100

Uniformity of weight
I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Thickness
Six tablets were examined for their thickness using vernier calipers and the mean thickness value was calculated.

Uniformity of Content
Twenty tablets selected randomly from each batch was weighed and powdered in pestle & mortar. The powdered tablet equivalent to 250mg drug in one tablet was taken and transferred in to a 50 mL volumetric flask and to this 25 mL of citro phosphate buffer pH 7.2 was added, sonicated for 10 minutes, shaken thoroughly for 15 minutes and then made the volume with citro phosphate buffer pH 7.2. Filter and further dilutions were made. The absorbances of these solutions were measured at 231 nm against solvent blank. The concentration of amoxicillin trihydrate in solution was estimated from the standard curve of Amoxicillin Trihydrate at 273 nm[10].

In-vitro disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Wetting time and water absorption ratio

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation was also determined. For measuring water absorption ratio the weight of the tablet was noted(Wb) and then the tablet was placed in the petridish.The wetted tablet was taken from petridish and reweighed(Wa).Then water absorption ratio(R) was determined according to the following equation : $R=100(Wa-Wb/Wb)$[6]

In vitro dispersion time

In vitro dispersion time is the time required to a tablet for its complete dispersion. It was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Dissolution study

The in-vitro dissolution studies were carried out using USP dissolution apparatus type-1 at 50 rpm in 900 ml of phosphate buffer at 37±0.5ºC. 10 ml sample was withdrawn at different time interval.The samples were filtered and amoxiciline content was analysed directly by UV/Vis spectrophotometer at 273nm.

RESULTS & DISCUSSION

In the present study amoxicillin trihydrate fast dissolving tablets were prepared in eight formulations with varying concentration of superdisintegrants i.e sodium starch glycolate and croscarmellose sodium. The swelling index of SSG and croscarmellose sodium were observed out in water, 0.1 N HCL and phosphate buffer pH 6.8 respectively. From the results it can be concluded that CCS has the highest swelling index value i.e 77.05 in water(table-2) than SSG in all the solvents viz. water, 0.1 N HCL and phosphate buffer pH and hence CCS can act as potential superdisintegrant for the development of fast dissolving tablets of amoxicillin Trihydrate. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. For a formulation to have good flow properties, θ should be ≤ 30º [11] and the angle of repose of precompressed blend of amoxicillin Trihydrate was found in the range 26.75^{o} to 28.31^{o},(table:3) indicating that the studied blend have excellent flow properties. The Bulk Density, Tapped Density for the granules of various formulations F1 to F8 were determined and their respective values of all the formulations ranged from 0.429 to 0.444 and 0.497 to 0.511 (table:3).Compressibility Index (%) was found in range from 11.87 to 15.38 (table:3).. These results obtained are in agreement with the desired value of compressibility index i.e 5-15 .Therefore, all the formulations studied (F1-F8) exhibited good compressibility index. All the tablet formulations (F1-F8) were evaluated in terms of various parameters *viz* hardness, % friability, weight variation, Uniformity of drug Content, thickness, (table4), wetting time and water absorption ratio (table 5).), disintegration time, *In vitro* dispersion time (table 5) *In Vitro* dissolution studies (table 6) and analysis of dissolution data, includes the values (Mean ± S.D) of all the parameters of F1-F8 tablet formulation prepared. Tablet weights were found in the range of 597.6 to 603.6 mg, friability between 0.19% to 0.31% hardness of all batches tablet were found to be in range of 4.23 to 4.50 Kg/cm^2, thickness between 4.785 to 4.84 mm, disintegration time was found to

be in range of 13.26 to 61.00 sec.The , *In Vitro* dispersion time was found to be in range of 16.00 to 70.33.00 sec., wetting time was found to be in range of 21.00 to 153.00 sec., water absorption ratio was found to be in range of 120.83 to 199.53 % sec., uniformity drug content between 96.60% to 99.36%,. Thus, all the physical parameters of the manually compressed tablets were quite within control limits.

In Vitro dissolution data of all tablet formulations was analyzed .Mean value of drug release is shown in Tables 6 and corresponding plot for dissolution profile of all tablet formulations is depicted in Fig.3. The comparative effect of two different superdisintegrants on the release profile of amoxicillin from formulations showed that formulation containing ,croscarmellose sodium found high (%) drug ralease profile of amoxicillin trihydrate from formulations while on the other hand SSG showed the less percent release profile of amoxicillin trihydrate from formulations at the comparative concentration used in the formulation of amoxicillin trihydrate. In case of formulation F1-F4 i.e. having SSG as superdisintegrant disintegration time as well as *in vitro* dispersion time decrease with increasing concentration of SSG (F1-F3) with the exception of F4 where, in disintegration time suddenly enhanced. The usual concentration employed in a formulation is between 2% and 8% with the optimum concentration about 4%[12]. This indicates that SSG as superdisintegrant should not to be used in higher concentration to formulate amoxicilline Trihydrate fast dissolving tablets. In case of formulation F7-F8 made from CCS no significant difference in disintegration time as well as in vitro dispersion time has been observed when CCS is used from 7.5-10%. It also indicates that lower concentration of CCS should be used (fig: 1)

Table 2
Swelling index for different superdisintegrants

Sr.No.	Name of superdisintegrants	Swelling index(%v/v)
1.	CCS	77.05±0.21(water)
	73.41±0.21(0.1N HCL)	
	71.35±1.32(Phos. buffer 6.8)	
2.	SSG	58.58±0.75(water)
	55.65±0.60(0.1N HCL)	
	54.44±0.79(Phos. buffer 6.8)	

Table 3
Micromeritic studies of tablet blends

Formulation code	Angle of reporse (ϕ)	Bulk density (g/mL)	Tapped density (g/mL)	Car-index (%)	Hausner ratio
F1	26.75	0.439	0.505	13.06	1.150
F2	26.86	0.434	0.508	14.62	1.170
F3	27.21	0.433	0.502	13.74	1.160
F4	26.91	0.444	0.505	12.07	1.137
F5	27.65	0.439	0.504	12.89	1.148
F6	28.31	0.436	0.511	14.67	1.174
F7	27.52	0.429	0.507	15.38	1.183
F8	28.10	0.438	0.497	11.87	1.135

Table4

Values of physical parameters and drug content for all tablet formulations of amoxicillin Trihydrate.

Formulation	Hardness (Kg/cm^2) (Mean ± S.D) n=6	Friability (%)	Thickness(mm) (Mean ± S.D) n=6	Weight (mg) (Mean ± S.D) n=10	Drug content (%)
F1	4.25±0.20	0.31	4.82± 0.02	600± 7.18	98.9
F2	4.23±0.18	0.30	4.81 ±0.04	603.6 ±6.60	98.5
F3	4.25±0.36	0.29	4.84 ±0.02	601.9±6.80	97.9
F4	4.50±0.27	0.21	4.78 ±0.03	600.4 ±7.56	99.3
F5	4.50 ±0.38	0.19	4.83 ±0.02	597.6±7.03	98.2
F6	4.40 ±0.23	0.26	4.81 ±0.03	602.5±7.11	99.3
F7	4.46 ±0.34	0.28	4.80 ±0.03	601.4±4.92	96.6
F8	4.41 ±0.12	0.27	4.83± 0.03	601.6± 7.78	98.1

Table5

Avg. value of Disintegration time, in vitro dispersion time , Wetting time and water absorption ratio.

Formulation code	Avg.Disintegration time(sec.) (±SD)	Avg. *In vitro* dispersion time (sec), (±SD)	Avg. wetting time (sec), (±SD)	Avg. Water absorption, (±SD)
	n=6	n=3	n=3	n=3
F1	61.00±1.55	70.33±4.02	153.00±2.16	120.83±0.62
F2	53.75±2.15	62.33±2.05	130.66±2.49	131.80±0.21
F3	50.66±1.88	57.00±0.81	102.00±2.49	144.6±0.71
F4	57.40±1.89	61.00±1.63	135.00±0.81	130.26±0.75
F5	19.41±1.15	22.00±0.816	67.66±2.05	153.7±0.35
F6	16.75±1.27	20.66±0.47	40.00±2.45	166.86±0.98
F7	14.43±0.62	18.33±1.24	28.00±0.81	186.20±0.57
F8	13.26±0.57	16.00±0.81	21.00±1.63	199.53±1.04

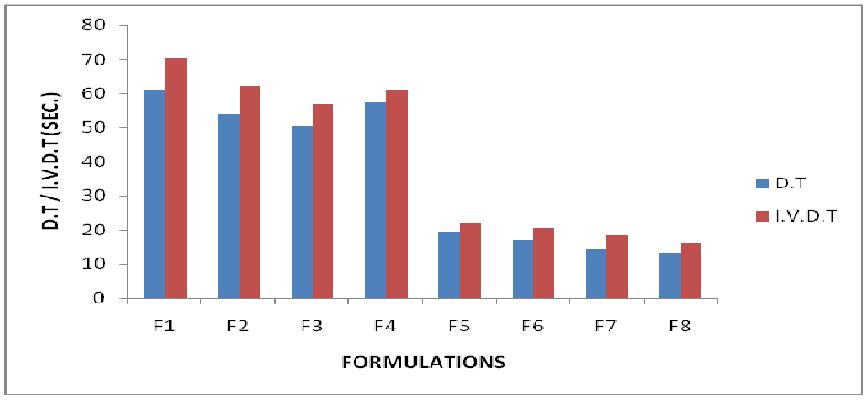

Figure 1

Histogram shows Disintegration time (D.T) (sec.) and In vitro dispersion time (I.V.D.T) of various formulations

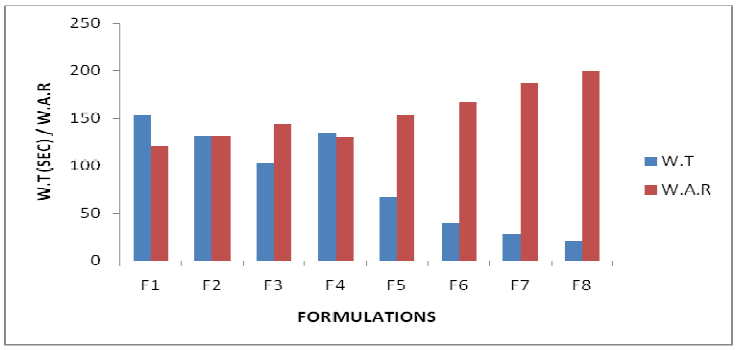

Figure 2
Histogram shows wetting time (W.T) (sec.) and water absorption ratio (W.A.R) of various formulations

Table: 6
Cumulative % drug release of formulations developed using CCS and SSG superdisintegrants at varied time

Formulation	Cummulative % drug release							
Time (min)→	0	1	2	5	10	15	20	25
F1	0	7.2	15.38	31.21	38.21	65.27	78.58	91.14
F2	0	8.46	16.11	36.09	43.69	67.2	79.1	92.2
F3	0	9	17.2	37.73	45.16	68.16	80.96	92.28
F4	0	10.26	19.91	39.75	45.77	72.19	82.52	94.57
F5	0	12.06	16.15	38.65	43.75	67.63	80.61	93.54
F6	0	13.32	16.7	40.11	45.95	69.13	81.23	94.89
F7	0	13.86	19.59	41.05	47.44	69.92	83.1	96.06
F8	0	14.4	21.04	42.69	49.28	72.86	86.25	99.78

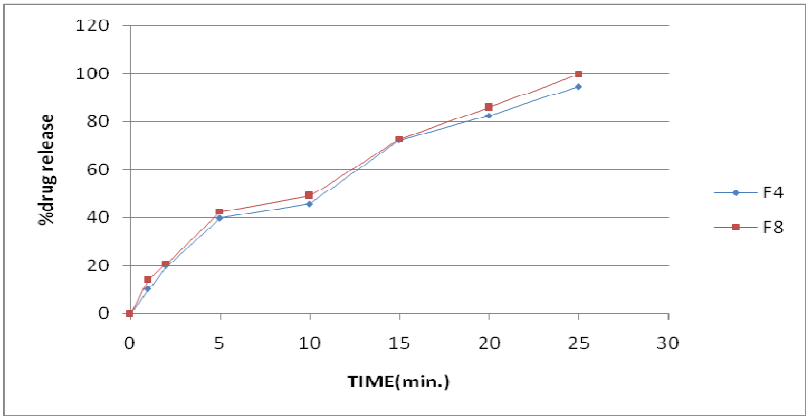

Figure 3
Cumulative % drug release from formulations containing SSG and croscarmellose sodium Disintegrant

CONCLUSION

Tablets and capsules, being most popular dosage form for oral delivery, have a major set back for elderly patient with dysphasia. To full fill this medical need, an attempt has been made in the present work to design and evaluate fast dissolving tablets of amoxicillin trihydrate using differ rent super disintegrants such as SSG, croscarmelose sodium.Fast dissolving drug delivery system (FDDDS) combines the advantages of both liquid and conventional tablet formulation. Amoxicillin Trihydrate is a semi-synthetic penicillin, an analogue of ampicillin, was chosen as the candidate drug for FDDDS for its broad spectrum of bactericidal activity against many gram-positive and gram-negative micro-organism From the results of these studied parameters it was concluded that formulation (F8) having 10% CCS and showed promising results than formulation (F4) having 10% SSG. FDT of amoxicillin Trihydrate in formulation F8 showed extremely fast dissolution rate than that of tablets of formulation F4.

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