Study of the effect of various super disintegrants on Amoxicillin trihydrate orally disintegrating tablets

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Abstract

Orally disintegrating tablets constitute an innovative approach to overcome the dysphagia in pediatric and geriatric patients and provide a quick onset of action. The current study was aimed to formulate and evaluate an orally disintegrating tablet containing Amoxicillin trihydrate using three types of Superdisintegrants: Croscarmellose sodium, crospovidone and sodium starch glycolate at three different concentrations (0.5, 1 and 2%) by direct compression method. The prepared tablets were evaluated for hardness, friability, weight uniformity, drug content uniformity, and disintegration time and drug dissolution rate. The results showed that Croscarmellose sodium at 0.5% gave a reduced disintegration time of 26s and a very high release rate of 97% in 20 min.

Keywords: *Orally disintegrating tablet; Amoxicillin trihydrate; Super disintegrant; Direct compression*.

I. Introduction

Oral drug delivery remains as the most popular and preferred route of administration due to its convenience of self-administration ease of ingestion, pain avoidance and easy manufacturing [1, 2]. However, the commonly used oral dosage forms like tablets and capsules encounter difficulty in swallowing (dysphagia) in case of pediatric, geriatric and psychiatric patients [3] and also in some others like bed ridden, active working and travelling patients who have no access to water [4]. For these reasons, orally disintegrating tablets (ODTs) technology, which make tablets dissolve or disintegrate in the oral cavity without any additional water intake [5] has attracted a renewed interest as a preferred approach to conventional tablets and capsules due to better patient compliance [6]. Several methods are used to fabricate ODTs, among them the direct compression method is highly used due to its simplicity, rapidity and cost-effectiveness. The ODTs can be fabricated using conventional manufacturing instrument with cheap raw materials, can be made into high dose and can be loaded with thermolabile drugs [7, 8].

To enhance the tablet disintegration and the rate of drug dissolution, Super disintegrants are often used in tablet formulations [7]. Among them, crospovidone, Croscarmellose sodium, and sodium starch glycolate are highly efficient at low concentration levels. The choice of a super disintegrant for a tablet formulation depends basically on the nature of the drug being used [9].

Amoxicillin is a penicillin derivative with a broad-spectrum against Gram-positive and Gram-negative bacteria. It is a extensively used as antibiotic for the treatment and prevention of respiratory, gastrointestinal, urinary and skin infections [10, 11]. In the current work, Amoxicillin trihydrate orally disintegrations tablets were developed using direct compression method. Three Superdisintegrants: crospovidone (PVP), Croscarmellose sodium (CCS), and sodium starch glycolate (SSG) were tested at three different concentrations (0.5%, 1% and 2% and the optimized formulation was selected based on the best dissolution profile and the fast disintegration time.

II. Materials And Methods

II.1. Materials

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Croscarmellose Sodium (CSC), Crospovidone (PVP), Sodium starch glycolate (SSG), microcrystalline cellulose (MCC) and magnesium

Stearate were supplied as gift samples from LDM Company, Constantine, Algeria.

II.2. Methods

II.2.1. Preparation of orally disintegrating tablets

The tablets were prepared by using direct compression method. Nine formulations (S_1, S_2, S_3, P_1, P_2, P_3, C_1, C_2, C_3) containing three types of Superdisintegrants (SSG, PVP and CSC) at three different concentrations (0.5%, 1% and 2%) were formulated according to the protocol shown in

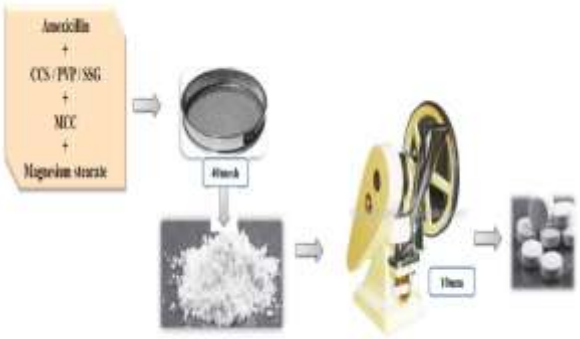

Figure 1. Protocol of ODTs preparation

The components of each formulation are showed in Table 1.

Table 1. Composition of Amoxicillin trihydrate ODTs.

Ingredients	S_1	S_2	S_3	P_1	P_2	P_3	C_1	C_2	C_3
Amoxicillin	250	250	250	250	250	250	250	250	250
SSG	2.5	4.5	9.5	-	-	-	-	-	-
PVP	-	-	-	2.5	4.5	9.5	-	-	-
CCS	-	-	-	-	-	-	2.5	4.5	9.5
Micro crystalline cellulose	187.5	185.5	181	187.5	185	181	187.5	185.5	181
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weigh t (mg)	450	450	450	450	450	450	450	450	450

All the ingredients were passed through 40 mesh sieve and mixed for about 10 min. The lubricated blends were compressed into tablets using 10 mm round concave punches to get tablet of 450 mg weight using an alternative tablet press (Deltalab, Single punch machine).

II.2.2 Evaluation of powder blend

- **Angle of repose**

Flow property of the powder blend for all the formulations was evaluated by determining the angle of repose and the compressibility index. The angle of repose (α) was measured by fixed funnel method. It was calculated according to the equation 1:

$$\tan \alpha = \frac{h}{R} \text{.....(1)}$$

Where, h is the height of the powder, R is the radius of the circle.

- **Compressibility index**

Carr's compressibility index for the powder blend was determined by using equation 2:

$$Carr'sindex\ (\%) = \frac{TBD-LBD}{TBD} \times 100 \text{.....(2)}$$

Where, TBD is the tapped bulk density, LBD is the loose bulk density

- **Hausner's ratio**

The Hausner's ratio was calculated using the equation 3:

$$\text{Hausner's ratio} = \frac{TBD}{LBD} \text{.....(3)}$$

II.2.3 ODT evaluation

- **Weight variation**

For assessing weight variation, twenty tablets were selected randomly and assessed individually using an analytical balance. The individual weights were

compared with the average weight for determination of weight variation.

❖ **Hardness and Friability**

Hardness of a sample of 10 ODTs from each formulation was measured using the Monsanto hardness tester (CALEVA/THT10).The friability of a sample of 20 ODTs from each formulation was measured utilizing a USP-type Roche friabilator (CALEVA/FT2). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and the percentage weight loss (friability) was calculated.

❖ **Drug content**

Tentablets were randomly selected from each formulation and pulverized to a fine powder. Weighed aliquots containing anamount of powder equivalent to a single dose were taken intriplicate and assayed for the drug content utilizing a UV-VISspectrophotometer at a wavelength of 228 nm.

❖ **In vitro disintegration time**

The *in vitro* disintegration test was carried out on six tablets using USP disintegration test apparatus (PHARMA TEST/PTZS) with distilled water at 37±0.5º and the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

❖ **In vitro dissolution study**

The *in vitro* dissolution study of the formulated ODTs of AMOX were studied in USP apparatus type II employing a paddle stirrer at 50 rpm using 900 ml of water at 37±0.5° as dissolution medium. Aliquots of dissolution medium (10 ml) were withdrawn at specific intervals of time and replaced with fresh dissolution medium at 5, 10, 15, 20 and 30 min. The samples were filtered through a 0.45 µ membrane filter. Absorbance of these solutions was measured at 228 nm using UV/Vis spectrophotometer. The percentage of drug release was calculated.

III. Results and discussion

The Results of powder blend evaluation were mentioned in Table 2. The values of angle of repose ranged from 30 to 35 and the compressibility index ranged from 7.46 to 13.84. Hausner's ratio was found to be between 1.06 and 1.11. These results indicate good flow property of all the formulations.

The results of ODT evaluation are illustrated in **Table 3**.All the formulations exhibited white color, odorless, convex in shape with smooth surface. Weight variation was found within the specification of the IP limits. Average weight of all formulations was found in the range of 440- 460 mg.

Hardness of the prepared tablets were in the range (40-50) kp; the friability of all formulations was found to be less than 1.0% and hence the tablets have sufficient mechanical strength and will not break during subsequent handling. The content uniformity of all the formulations was found in the range of 89-102%, hence AMOX was uniformly distributed in all tablets.

From **figure 2**, it is clear that the SGS amount had a remarkable effect on the release rate of AMOX. As the amount of starch was increased from 0.5% to 2%, there was an enhancement in the release rate during all the study. It was observed that with increase in concentration of starch, the release rate of drug was increased. Similar results have been already documented [9].The formulation **S_3** has showed the best dissolution profile compared with S_1 and S_2.

According to **Figure 3**, the amount of Amox released increases with the increase in PVP concentration in the first 10 min. The amount of drug released in 5min QPA% (5min) is 50%, 59% and 67% for P_1, P_2 and P_3 which contain 0.5%, 1% and 2% of PVP respectively. This is related to the capillary effect of PVP, as its amount increases, the penetration of water inside the tablet increases and therefore Amoxicillin leaves the tablet quickly. Similar results were already found [12].

However, limited drug release was observed after 20 min for P_3 which contains 2% of PVP. This may be explained by the fact that the PVP, after a critical concentration, forms a viscous layer which will block the pores, making the inside of the tablet inaccessible to water and thus the release of AMOX decreases. Similar results were found in [13], where PVP at higher concentration (15%) delayed the wetting and the disintegration of tablets containing berberine hydrochloride [13]. Pandya and his coworkers related the decrease in celecoxib dissolution rate to the gel layer formed by a large amount of PVP which hindered further water

penetration into the tablets [14]. Shirwalker and his coworkers found that PVP 10%w/w is the optimum level, after these concentration, a decrease in dissolution rate was observed due to the blockage of pores [15].

The same phenomenon occurred in the case of croscarmellose sodium where the release of the drug decreased after 15min for formulas C_2 and C_3 which contain 1% and 2% of CSC respectively (**Figure 4**). Similar release profile was found in [15] where 8%w/w was the optimum level. At high concentrations, the CSC forms a gel which delays the release of AMOX. So C_1 was chosen as the optimal formula for CSC.

The effectiveness of super disintegrants on drug release profile was in the order CSC> PVP> Starch. According to the table, CSC was more efficient than PVP. This can be explained by the hydrophobicity of PVP [16]. The same result was found in [17].

Regarding the time of disintegration of the formulations (S_3, P_2 and C_1), the total disintegration of Amox tablets was achieved in less than 30s for C_1 and P_2, while it was very slow for S_3. This confirms the effectiveness of PVP and CSC over starch. The decay time of P_2 is somewhat reduced compared to C_1, this is perhaps explained by the fact that PVP has a more porous structure than CSC, it absorbs water quickly and therefore disintegrates first [16]. These results have been proven by other studies [18].

Despite the efficiency of the PVP, the formula C_1 which contains CSC at 0.5% was chosen as the optimum formula basing on the release rate results as mentioned in **Figure 5.**

Table 2. Evaluation of powder blend.

Formulation	Angle of repose	Carr index	Hausner ratio
S1	33	12.12	1.11
S2	32	13.84	1.08
S3	30	7.46	1.07
P1	35	11.59	1.10
P2	30	13.50	1.06
P3	32	12.12	1.11
C1	33	13.50	1.06
C2	31	13.04	1.10
C3	32	13.63	1.10

Table 3. Physical parameters of Amoxicillin trihydrate ODTs.

Formulation	Hardness (Kp)	Friability (%)	Weight uniformity (mg)	Drug content (%)
S1	41 ± 2.1	0.52	445 ± 2.3	100 ± 3.2
S2	42 ± 0.6	0.41	449 ± 2.3	99 ± 2.5
S3	45 ± 2.1	0.62	452 ± 1.3	98 ± 2.5
P1	45 ± 0.9	0.55	455 ± 1.3	99 ± 1.8
P2	44 ± 1.1	0.52	448 ± 2.6	89 ± 0.2
P3	45 ± 1.8	0.39	449 ± 4.2	98 ± 2.5
C1	42 ± 0.7	0.64	447 ± 2.3	97 ± 0.4
C2	45 ± 0.7	0.52	452 ± 1.2	102 ± 1.2
C3	42 ± 2.3	0.51	455 ± 1.6	100 ± 0.5

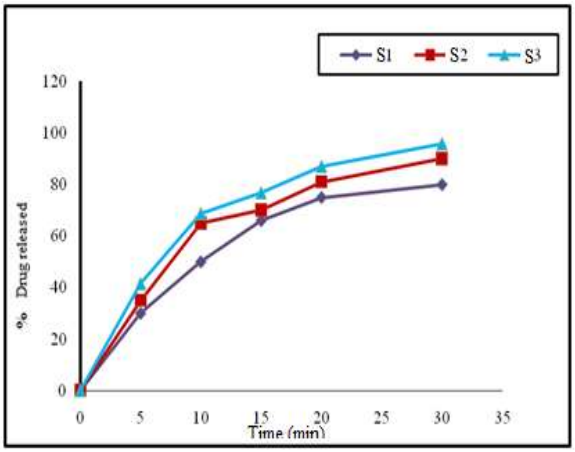

Figure 2. Effect of sodium starch glycolate amount on drug release

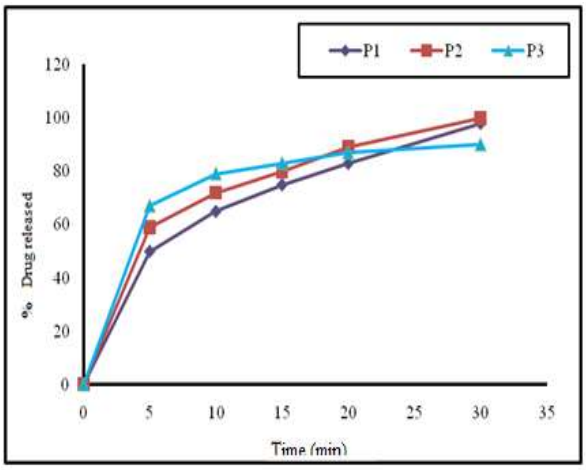

Figure 3. Effect of Crospovidone amount on drug release

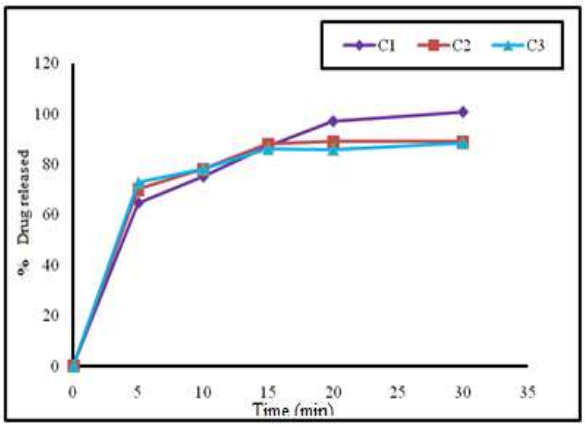

Figure 4. Effect of croscarmellose sodium amount on drug release

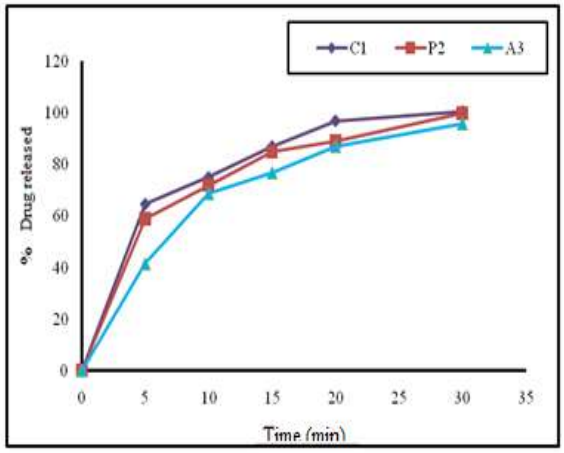

Figure 5. Effect of type of Superdisintegrant on drug release

Conclusion

Fast disintegrating tablets are gaining importance as a new drug delivery system and appear to be one of the most popular and widely accepted pharmaceutical forms for pediatric and geriatric patients. The aim of our work was to formulate ODTs based on Amoxicillin, by direct compression, to study the effect of type and amount of superdisintegrant on the release of the active ingredient as well as the evaluation of the optimal formula. It has been found that it is not always true that the increase in the concentration of the superdisintegrant promotes an increase in the release of the active principle, in our study we have found that this effect is limited to a certain concentration, so we recommend keeping its amount in an optimal limit to achieve a better release of the active ingredient. Croscarmellose sodium at a concentration of 0.5% gave a reduced disintegration time of 26 ± 1.4s and a very high release rate of 97% in 20 min. Finally, this work opens the field to more experimental study about the long-term stability study and the in vivo behavior of this formulation.

References

[1] Abay, Ugurlu, 2015. Orally Disintegrating Tablets: A Short Review. J. Pharm. Drug Dev. 3. https://doi.org/10.15744/2348-9782.3.303

[9] Ajaykumar, B., Y, R.B., Sasikanth, K., Aswini, G.L., Srinivas, D., Pg, D., 2013. Study on Influence of Super Disintegrants and Lubricants on the Dissolution Rate of Atenolol Tablets 1, 52–55.

[3] Alğin Yapar, E., 2014. Orally disintegrating tablets: An overview. J. Appl. Pharm. Sci. 4, 118–125. https://doi.org/10.7324/JAPS.2014.40219

[18] Ann Druffner, Wayne Camarco, D.R., 2006. Selecting Superdisintegrants for Orally Disintegrating Tablet Formulations. Pharm. Technol.

[12] Chaulang, G., Patil, K., Ghodke, D., Yeole, P., Bhosale, A., Hardikar, S., 2008. Effect of some physical parameters and crospovidone on directly compressed frusemide tablets. Asian J. Pharm. 2, 235. https://doi.org/10.4103/0973-8398.45038

[6] Ganesh, N., Deshpande, K., 2011. Orodispersible Tablets: An Overview of Formulation and Technology. Int J Pharma Bio Sci 2, 726–34.

[13] Hu, X., Li, Y., Zhang, E., Wang, X., Xing, M., Wang, Q., Lei, J., Huang, H., 2013. Preparation and Evaluation of Orally Disintegrating Tablets Containing Taste-Masked Microcapsules of Berberine Hydrochloride. AAPS PharmSciTech 14, 29–37. https://doi.org/10.1208/s12249-012-9880-6

[16] Mohanachandran, P.S., Sindhumol, P.G., Kiran, T.S., 2011. Superdisintegrants: An overview. Int. J. Pharm. Sci. Rev. Res. 6, 105–109.

[7] Nagar, P., Singh, K., Chauhan, I., Verma, M., Yasir, M., Khan, a, Sharma, R., Gupta, N., 2011. Orally disintegrating tablets: formulation, preparation techniques and evaluation. J. Appl. Pharm. Sci. 1, 35–45.

[5] Pandey, P., Dahiya, M., 2016. Oral Disintegrating Tablets: A Review. Int. J. Pharma Res. Rev. Mand. Dahiya et.al IJPRR 5, 50–62.

[14] Pandya, V.M., Patel, D.J., Patel, J.K., Patel, R.P., 2009. Formulation, Characterization, and Optimization of Fast-Dissolve Tablets Containing Celecoxib Solid Dispersion. Dissolution Technol. 16, 22–27. https://doi.org/10.14227/DT160409P22

[8] Parkash, V., Maan, S., Deepika, Yadav, S., Hemlata, Jogpal, V., 2011. Fast disintegrating tablets: Opportunity in drug delivery system. J. Adv. Pharm. Technol. Res. 2, 223. https://doi.org/10.4103/2231-4040.90877

[10] Saptarini, N.M., 2012. Evaluation of Content and Dissolution Profile of Generic Amoxicillin Tablets 3, 64–66.

[4] Seager, H., 1998. Drug- delivery Products and the Zydis Fast- dissolving Dosage Form. J. Pharm. Pharmacol. 50, 375–82.

[15] Shirwaikar AA, R.A., 2004. Fast disintegrating tablets of atenolol by dry granulation method. Indian J Pharm Sci 66, 422–6.

[17] Tanuwijaya, J., Karsono, 2013. The effects of crospovidone and croscarmellose sodium as superdisintegrants on the characteristics of piroxicam nanoparticles ODT (orally disintegrating tablet). Int. J. PharmTech Res. 5, 1590–1597 ·.

[2] Velmurugan, S., Vinushitha, S., 2010. Oral disintegrating tablets: An overview. Int. J. Chem. Pharm. Sci. 1, 1–12.

[11] Vidyadhara, S., Sasidhar, R.L.C., Deepti, B., Wilwin, E., Sowjanyalakshmi, B., 2015. Formulation and evaluation of Amoxicillin Trihydrate Lozenges. Dhaka Univ. J. Pharm. Sci. 14, 61–70.