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Effect of superdisintegrants and their mode of incorporation on disintegration time and release profile of carbamazepine from immediate release tablet

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ABSTRACT

In this experiment the effect of mode of incorporation of some superdisintegrants such as sodium starch glycolate, croscarmellose sodium, crospovidone (kollidon CL), ludiflash and Xanthan gum (XG) on dissolution profile and disintegration time of carbamazepine (CBZ), apoorly water soluble drug was studied. The superdisintegrants were incorporated by extragranularly, intragranularly and in direct compression method. Different amount of superdisintegrants (1%, 3% and 6%) was incorporated in different formulations whereas all the other excipients as well as the active drug remained same. The results indicated that sodium starch glycolate, when incorporated extragranularly in wet granulation method significantly enhanced the release profile of CBZ. Kollidon CL was the most effective superdisintegrant in decreasing disintegration time of different tablet formulations (1.95 minutes when extragranularly incorporated). On the other hand, tablets prepared with SSG were found most effective in % drug release irrespective of its mode of incorporation (99.99% when extragranularly incorporated and 99.75 when intragranularly incorporated within one hour). Tablets prepared by direct compression method also showed similar drug release with other methods but tablet hardness was found lower. So addition of superdisintegrants in tablet formulation may be an effective technique to comply compendial drug release.

INTRODUCTION

Carbamazepine (CBZ) was originally used for the treatment of trigeminal neuralgia and is still employed for this purpose. CBZ has been shown to be particularly effective for the treatment of complex partial psychomotor or temporal lobeseizures, as well as generalized convulsive or tonic-clonic seizures. CBZ is one of the major anti-convulsant drugs and considered by many clinicians as the drug of first choice in the treatment of focal seizures and has been shown to be as effective as an anti-convulsant in the treatment of partial and grandmal seizures (Mackichan et al., 1981). CBZ is readily soluble in non-polar nonpolar solvents but sparingly soluble in alcohol and 5-acetone (Mackichan et al., 1981; Aboul-Enein et al., 1980; British Pharmacopoeia, 2005). The process of dissolution plays a vital role in liberation a drug from its dosage form and making it available for subsequent gastrointestinal absorption. Disintegration, which breaks down a tablet into granules and small fragments, facilitates dissolution by increasing the surface area for drug release. Therefore, besides the content of active ingredient per unit, disintegration and dissolution properties and extremely important for quality control of tablet dosage forms. These two physical processes are affected by many factors including formulation components and manufacturing methods (Ancel and Popovich, 1990). Tablet disintegration and dissolution processes are intimately connected to each other and it is a general assumption that dissolution characteristics of tablets can be predicted by knowing the disintegration time. Disintegrants are generally added in solid dosage form to decrease the disintegration time with the intention to increase drug dissolution. Disintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

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Because of the increased demands for faster dissolution requirements, new generation of disintegrants which are known as super disintegrants (SD) are now available. The super disintegrants can be added to the formulation internally or externally. In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules (Bhowmik et al., 2010). Commonly used superdisintegrants are crosslinked cellulose eg: croscarmellose sodium, ac-di sol, primellose, crosslinked pvp, kollidone, polyplasdone, crosslinked starch such as sodium starch glycolate, explotab, primogel etc.

The purpose of the present study was to compare the effect of mode of addition of different superdisintegrants (with various concentration) and evaluate their effect on dissolution of CBZ in water with 1% SLS as specified in the compendia. CBZ is a low water soluble drug with high permeability, hence is classified as BCS (Biopharmaceutical Classification System) Class II drug adopted by USFDA. Being a poorly water soluble drug it has less affinity to water and is always hydrophobic in nature. The solubility and dissolution behavior of a drug is an important factor for oral bioavailability. Superdisintegrants are added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Previously many attempts were taken to improve the bioavailability of CBZ like microencapsulation, solid dispersion etc. Here the effects of superdisintegrants on the dissolution of CBZ were observed.

EXPERIMENTAL

Materials

CBZ was presented by ACI Pharmaceuticals Ltd. Bangladesh. Povidone K30 (Colorcon, USA), Sodium Starch Glycolate (Colorcon, USA), Croscarmellose Sodium (Ming Ti, Taiwan), Ludiflash (BASF,Germany), Sodium Lauryl Sulphate (Merck, Germany) were purchased from the source indicated. Lactose, Avicel PH 102, Magnesium stearate, purified talc were of BP grade.

Preparation of tablets

In this experiment the effect of some superdisintegrants on dissolution profile and disintegration time of carbamazepine (CBZ) tablet was studied. Tablets of CBZ were prepared using wet granulation and direct compression techniques.

Different amount of superdisintegrants (1%, 3% and 6%) was used in different tablet formulations whereas all other excipients as well as the active drug were same. (Table 1) superdisintegrants such as sodium starch glycolate, croscarmellose sodium; crospovidone (kollidon CL), ludiflash and xanthan gum (XG) were incorporated by extragranularly, intragranularly and in direct compression method. In external addition method, granules were prepared first and then superdisintegrants were added to the sized granules prior to compression. In Internal addition method, the superdisintegrants were mixed with other components before wetting the powder mixture with the granulating fluid. In direct compression method all the components were mixed and compressed.

Calculated amount (required to prepare a 50 tablet batch) of the drug (carbamazepine) and excipients were weighed and mixed thoroughly. Sufficient volume of the specified granulating agent (purified water) was added slowly and mixed. When enough cohesiveness was obtained, the granules were dried at 60°C for 2 hours in a tray dryer and there after kept in desiccators for 24 hours at room temperature. The LOD of the granules was kept between 2.5 to 3.0%. The dried granules were collected and screened through a #20 mesh sieve. Prior to compression, all prepared granules were evaluated for several tests such as bulk density, compressibility index and angle of repose.

Appropriate amount of the granules or powder mixture was weighed and then compressed using a laboratory hydraulic press equipped with 11 mm, round shaped punch and die set. All compressed tablets were stored in an airtight container at room temperature for further study.

Table 1: General formula of the prepared tablets.

Ingredients	Amount per tablet
Carbamazipine	200 mg
Lactose	65 mg
Avicel 102	200 mg
Povidone K30	20 mg
Magnesium stearate	1 mg
Purified Talc	1mg
Superdisintegrants	1%, 3% or 6%

Determination of disintegration time

Disintegration time of the prepared tablets were measured in 900 ml distilled water containing 1% SLS (sodium lauryl sulphate) with disc at 37^0C, using Disintegration Test Apparatus (VTD-2, India). Disintegration time of 6 individual tablets was recorded for each formulation and the average DT was calculated.

In vitro dissolution studies

In-vitro dissolution study of CBZ tablets were studied in USP (XXIII) Dissolution Test Apparatus (TDT- 06T, ELECTROLAB, India) employing rotating paddle. The in-vitro release of CBZ was studied for 1 hour in distilled water containing 1% SLS. An amount of 900 ml of the dissolution fluid was used at 37°±0.5°C with a stirrer speed of 75 rpm. Eight tablets were used in each test. The sample solution was analyzed at 288 nm for CBZ by a Shimadzu UV-1240 UV/Visible double beam spectrophotometer (Shimadzu, Japan). Drug dissolved at specified time periods was plotted as percent release versus time.

RESULTS AND DISCUSSION

Characterization of granules

The prepared granules of different formulations were free flowing with irregular shape. The bulk densities of granules with

internal addition of superdisintegrants were quite higher than those of other granules. This may be due to the presence of less amount of fine powder. The results of compressibility index (%) ranged from 12.54 to 20.14. The results of angle of repose ranged from 24° to 28°. The results of angle of repose (<30°) indicate good flow properties of granules which was supported the results found from compressibility index.

Physicochemical evaluation of tablets

The weight variation, disintegration time and % drug release after one hour for each formulation are shown in Table 2. The thickness of the tablets were found between 4.21 ± 0.01 mm to 4.31 ± 0.09 mm, hardness of the tablets ranged from 3.69 ± 0.42 kg/cm^2 to 8.29 ± 0.24 kg/cm^2 and friability ranged from 0.10% to 0.17%. The drug content of every formulation was found about to 100% of labeled content.

Effect of mode of incorporation of superdisintegrants on disintegration time (DT) of carbamazipine tablets

It was observed that DT of formulation without any superdisintegrant was 44.69 (Table 3) minutes and it decreases when superdisintegrants were incorporated in the formulation. Superdisintegrants which were added to the drug formulations facilitated the breakup or disintegration of tablet content into smaller particles that dissolved more rapidly. From table 2 and 3 it is clear that nature and method of incorporation of superdisintegrants has a great effect on the DT of carbamazipine tablets. In this case, lowest DT for 1% extragranular incorporation of superdisintegrants was 6.76 ± 0.41 min in case of croscarmellose sodium and due to the increase (6%) of croscarmellose sodium DT decreased up to 2.48 ± 0.58 min. On the other hand intragranullar incorporation of superdisintegrants was found less effective than extragranular incorporation. In this case Lowest DT for 1% extragranular incorporation of superdisintegrants was 9.68 ± 0.4 min in case of Croscarmellose sodium and due to the increase (6%) of superdisintegrants DT decreases upto 3.05 ± 0. 19 min. Intragranullar incorporation of superdisintegrants which was added before wetting of powder and as part of the granulation process the powder passed through wetting and drying processes. This may be responsible for the reduced activity of the superdisintegrants. Since the disintegrant used extragranularly did not passed through wetting and drying process, tends to retain good disintegration activity (Parthiban et al., 2011). In case of direct compression technique, DT was found only 5.50 ± 0.51min (without superdisintegrants) and 0.7 ± 0.51 min with 1% Ludiflash. superdisintegrants were found more active in case direct compression technique as there is no wetting process in this technique. But tablet hardness was relatively lower in case of direct compression technique.

Effect of xanthan gum on DT and dissolution of carbamazine tablets

It was observed from Table 3 that DT of formulations with 1% XG was 18.05 and 16.15 minutes in case of extragranular and intragranular incorporation respectively. But when 6% XG was added extragranularly and intragranularly, the DT of respective formulation became 48.625 and 37.75 minutes. So, it can be assumed that here XG did not behave as a superdisintegrant rather than it acted as binder which holds the drug and other excepients hence, prevented the breakdown of the formulations. So, we can say XG has less disintegration activity when used in low concentration but it has no disintegration activity at higher concentration and it increases the disintegration time by resisting the breakup of tablet. Disintegration activity of XG at low concentration may be due to greater swelling capacity (Bhowmik et al., 2010).

Table 2: weight variation, disintegration time (DT) and drug release of carbamazipine tablets containing sodium starch glycolate, croscarmellose sodium and Kollidon CL as superdisintegrants (EG = Extragranular, IG = Intragranular, DC = Direct compression).

Superdisintegrant (S.D)	Mode of S.D addition	Concentration of SD	Weight (mg)	DT (mins)	% Release after 1 hr.
Sodium starch glycolate (SSG)	EG	1%	490.18 ± 0.1	10.08 ± 0.38	97.42 ± 0.3
		3%	501.5 ± 0.3	7.05 ± .02	98.69 ± 0.25
		6%	517.32 ± 0.12	3.19 ± 0.2	99.90 ± 0.32
	IG	1%	491.13 ± 0.2	11.03 ± 0.5	88.98 ± 0.42
		3%	501.2 ± 0.31	6.05 ± 0.45	99.34 ± 0.4
		6%	515.01 ± 0.3	6 ± 0.36	99.75 ± 0.29
	DC	1%	492.17 ± 0.22	1.47 ± 0.21	97.52 ± 0.3
		3%	500.9 ± 0.4	1 ± 0.32	99.88 ± 0.36
		6%	516.23 ± 0.36	1.4 ± 0.39	99.83 ± 0.3
Croscarmellose sodium (CCS)	EG	1%	492 ± 0.27	6.76 ± 0.41	88.96 ± 0.4
		3%	502 ± 0.16	5.04 ± 0.7	88.10 ± 0.35
		6%	517 ± 0.28	2.48 ± 0.58	93.72 ± 0.5
	IG	1%	491.25 ± 0.27	9.68 ± 0.4	87.09 ± 0.52
		3%	501.96 ± 0.39	5.43 ± 0.36	85.37 ± 0.43
		6%	516.94 ± 0.34	3.05 ± 0. 19	89.94 ± 0.39
	DC	1%	492.03 ± 0.4	1.34 ± 0.3	94.84 ± 0.3
		3%	502.12 ± 0.41	1.83 ± 0.32	97.07 ± 0.29
		6%	517.01 ± 0.42	1.78 ± 0.36	99.56 ± 0.27
Kollidone CL (KCL)	EG	1%	492.23 ± 0.3	21.55 ± 0.4	30.68 ± 0.4
		3%	501.73 ± 0.27	3.33 ± 0.41	84.98 ± 0.62
		6%	516.86 ± 0.41	1.95 ± 0.44	99.67 ± 0.64
	IG	1%	491.53 ± 0.47	24.5 ± 0.7	25.95 ± 0.7
		3%	502.11 ± 0.22	10.08 ± 0.68	82.59 ± 0.54
		6%	516.98 ± 0.32	5.4 ± 0.5	95.72 ± 0.42
	DC	1%	492.03 ± 0.51	0.75 ± 0.9	88.61 ± 0.33
		3%	502.04 ± 0.29	0.75 ± 0.9	93.82 ± 0.64
		6%	517.13 ± 0.4	0.39 ± 0.82	99.94 ± 0.52

Effect of superdisintegrant on % drug release from carbamazipine tablets

Superdisintrgrants were also found to increase the percent drug release from different formulation. Fig. 1. Represents the dissolution profile of different formulation. Tablets prepared

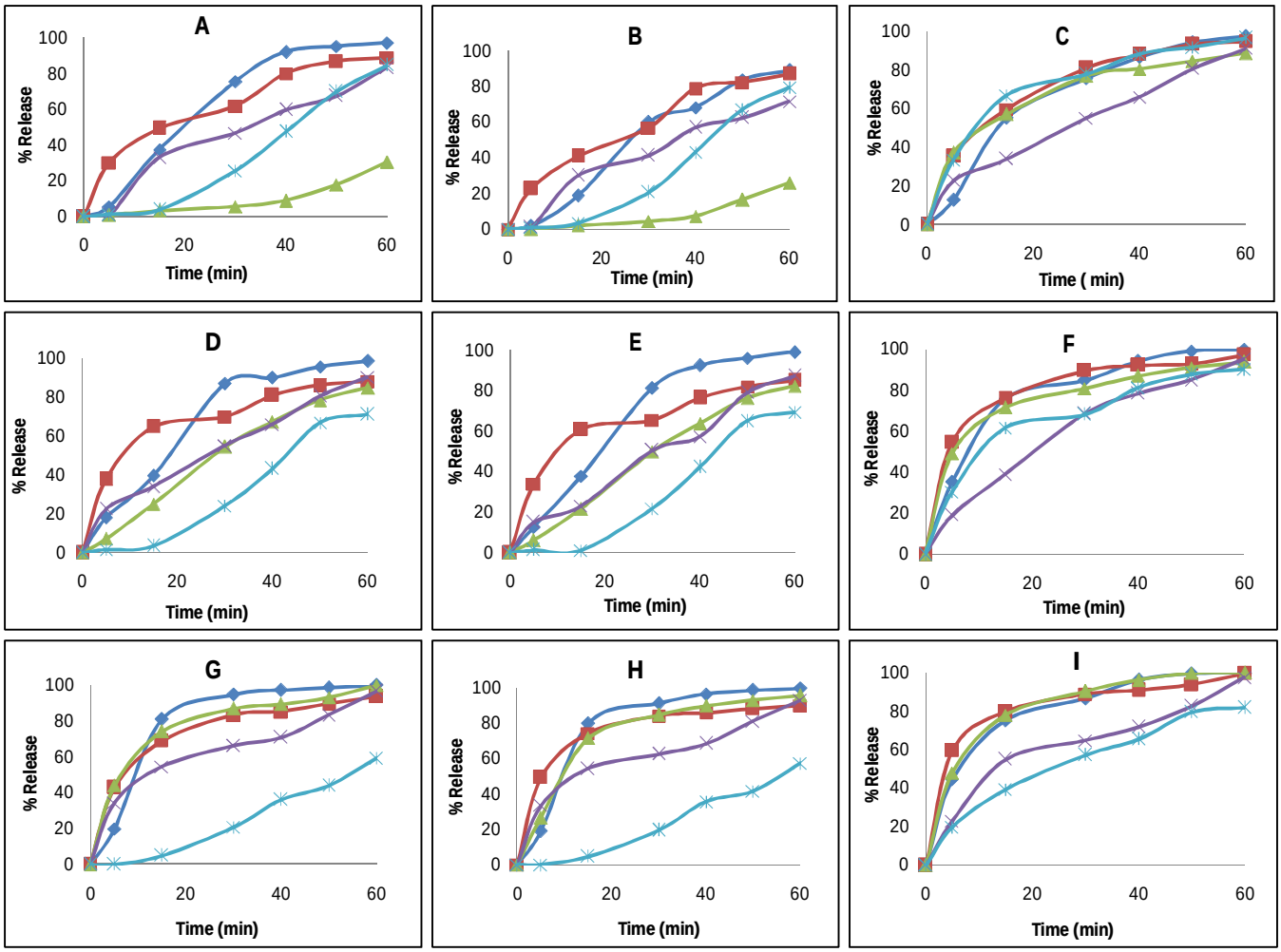

Fig. 1: Dissolution profile of different formulation. (A,B,C Formulation with 1% superdisintegrants; D, E, F contain 3% and G, H, I contain 6% superdisintegrants. A, D, G represent extragranular incorporation of superdisintegrants. B, E, H represent intragranular incorporation of superdisintegrants whereas C, F, I represent directly compressible tablets. ■ = CCS, ♦ = SSG, ▲ = KCL, × = Ludiflash, × = XG)

without superdisintegrants by wet granulation technique released only 6% CBZ after one hour. This may be due to the less water solubility of the drug and higher DT of tablets (44.69 ± 0.25 min). This does not comply the USP requirements for CBZ tablet. Addition of superdisintegrant by either intragranular or extragranular method increases the percent drug release. This may be due to the lower DT of tablets that facilitates the breakup of tablet content into smaller particles that dissolved more rapidly. The effect of sodium starch glycolate, croscarmellose sodium, ludiflash on drug dissolution was almost similar added either by extragranullarly or intragranularly but Kollidon CL released only 25.95 ± 0.7% drug after one hour when 1% Kollidon CL was added. But it released 95.72 ± 0.42% drug when when 6% Kollidon CL was added in the formulation. The behavior of XG on drug release was quite different. Drug release was decreased when higher amount of XG added with the formulation. 84.90 ± 0.57% drug was released after one hour for addition of 1% XG on the other hand 59.23 ± 0.39 % drug was released within same time when 6% XG was added. Tablets prepared by direct compression without SD released 53 ± 0.6% drug within one hour (Table 2) and addition of SD increased dissolution which was shown in fig 1. Higher amount of drug was found to release in case of direct compression method. This may the lower disintegration time of tablets.

CONCLUSION

Low dissolution and bioavailability is a problem for a water insoluble drug. This problem can be overcome by adding superdisintegrants in the formulation. Direct compression method is the most effective technique for the incorporation of superdisintegrants to increase the dissolution rate. But due to lower hardness and higher friability the technique may not be acceptable in all the cases. However extragranular incorporation of superdisintegrants may be an effective method for decreasing disintegration time of tablets with optimum physical properties.

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