EFFECT OF MODE OF ADDITION OF DISINTEGRANTS ON DISSOLUTION OF MODEL DRUG FROM WET GRANULATION TABLETS

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ABSTRACT

The purpose of the study was to formulate immediate release tablets using various types of disintegrants (crospovidone, sodium starch glycolate and sodium carboxymethylcellulose), in order to investigate the effect of mode of incorporation of disintegrants on release mechanism from tablets. Acetaminophen, a poor soluble drug was used as a model drug to evaluate its release characteristics from different formulations. The USP paddle method was selected to perform the dissolution profiles carried out by USP apparatus 2 (paddle) at 50 rpm in 900 ml phosphate buffer pH 5.8. Successive dissolution time, time required for 25%, 50% and 80% of the drug release (T_{25}%, T_{50}%, T_{80}%) was used to compare the dissolution results. A One way analysis of variance (ANOVA) was used to interpret the result. Statistically significant differences were found among the drug release profile from all the formulations except mode of addition of crosspovidone. At a fixed amount of disintegrants, extragranular mode of addition seemed to be the best mode of incorporation. The best release was achieved with the crospovidone containing formulations. The T_{50} and T_{80} values were indicative of the fact that the drug release was faster from tablet formulations containing crosspovidone. The drug release was very much negligible difference by the mode of crospovidone addition. Two formulations found very small T_{50} and T_{80} values indicating very much faster release. From the all formulations corresponded extragranular mode of addition could be the best mode of incorporation. The drug release was unaffected by the mode of crospovidone addition. The mode of incorporation of disintegrants suggested enchancing the release of poor soluble drugs.

Key words: Acetaminophen, disintegrants, wet granulation, intragranularly, extragranularly

INTRODUCTION

Disintegrants are substances or mixture of substances added the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants [1,2]. Kornblurn et al [3] has reported the cross linked polyvinyl pyrrolidone and evaluated as tablet disintegrants and compared to starch USP and alginic acid. The capillary activity of crospovidone for water is responsible for its tablet disintegration property. Cross linked PVP has maximum moisture absorption and hydration capacity and can be considered for the selection of new disintegrant. They possess apparent binding property resulting in low percent of tablet friability, where it is employed as disintegrant even in low concentration 0.5 to 5 percent. The sodium starch glycolate was incorporated as a super disintegrant in the enteric coated antigen micro spheres and was studied by Zhang et al. [4]. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. In more recent years, increasing attention has been paid to formulating fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth [5-7].

The disintegrant can be incorporated either intragranularly, extragranularly or it can be distributed both intra and extragranularly. Although many reports are available in the literature where superdisintegrants in wet granulated tablets have been examined using single mode of incorporation [8-11] not many reports are available in literature, where the effect of mode of superdisintegrant incorporation on the dissolution of drugs has been fully investigated.

Lang (1982) [12] showed that an equal distribution of superdisintegrant in both intragranular and extragranular phases resulted in better dissolution than total incorporation. Therefore, there is contradiction in the literature as

to where the superdisintegrant should be distributed for the tablet dissolution to be optimized. The purpose of the present study is to compare the effect of mode of addition of different superdisintegrant and evaluate their effect on dissolution of poor soluble drugs.

Superdisintegrants (when not used in tablets) have been shown to be behave differently when exposed to different pH environment [13]. Further, it has been shown that Sodium starch glycolate (SSG) can influence the disintegration time of acetaminophen tablets depending on whether gastric juice or water is used as the medium (Guyot-Hermann and Ringard, 1981) [14] and Vadas et al. (1984) [15] showed that croscarmellose sodium was insensitive to change of pH of medium. To characterize the drug release rate in different experimental conditions,$T_{25\%}$, $T_{50\%}$ (mean dissolution time) and $T_{80\%}$ were calculated from dissolution data according to the following equations: $T_{25\%} = (0.25/k)^{1/n}$, $T_{50\%} = (0.5/k)^{1/n}$, $T_{80\%} = (0.8/k)^{1/n}$ where K is the kinetic constant and n is the exponent that characterize the mechanism of drug release.

EXPERIMENTAL

Materials

Acetaminophen raw material was collected from Dr. Reddys laboratory India, as a specimen sample. Other materials used in this study were lactose (Hilmar Ingradients, U.S.A), povidone K30 (Merck KGaA, germany), Crospovidone (Merck KGaA, germany), Sodium Starch Glycolate (Merck KGaA, germany), Sodium Carboxy Methyl Cellulose (Shengtai medicine co., Ltd, China), Avicel pH 101 was purchased from Ming Tai Chemical Co.Ltd., (Taiwan), Magnesium stearate and Purified Talc was procured from Hanua Chemicals Limited, (Japan), and Aerosil was procured from CABOT, India. All other reagents used were analytical grade.

Methods

Preparation of immediate release Acetaminophen tablets:

The general formula of the tablets prepared using the three drugs is given in Table 1.

Three disintigrants Crospovidone (CP), Sodium carboxymethylcellulose (Na CMC) and Sodium Starch Glycolate (SSG) were used by altering their use extrgranularly (EG) and intragranularly (IG). Also sample with using the same disintigrant extragranular and intragranular were prepared. In all the formulations all other tableting components were kept same in same concentration except Avicel pH 101. The quantity of water for wet massing varied to obtain suitable granules.

All the formulations (A1- A6), the formulations A1 and A2 containing crospovidone, A3 and A4 containing sodium starch glycolate, A5 and A6, containing sodium carboxymethylcellulose intragranularly (IG) and extragranularly (EG) respectively were prepared by wet granulation method as Acetaminophen is a fluffy material having particle distribution of 10-15 µm there of adequate flow for direct compression were not readily available. The tablets contain 250 mg of Acetaminophen with using Aerosil and purified talc and Mg. stearate. Lactose and Avicel were used as diluents to keep the tablet weight 350mg. 3% povidone k30 was used as binder to prepare granules of suitable strength. Materials were accurately weighted using electric balance. Lactose was passed through a 20 mesh sieve. A 12% solution of povidone k30 was prepared with sufficient water. Povidone K 30 solution was added with the powders to prepare suitable granules (additional water was added to prepare suitable granules). Granules were dried in a tray dryer at 60°c temp until a LOD of 6 – 7 was observed. Granules were passed through a 16 mesh sieve. Granules were dried until a final LOD of 3-3.5 is observed. Granules were passed through a 20 mesh sieve. Lubricants were passed through a 40 mesh sieve and mixed with the granules for 3 minutes. Tablets were compressed using Lota press compression machine (D tooling punch) 15mm caplet shaped punch keeping weight of 350 mg.

Physical evaluation of tablets

Weight variation

20 tablets from each formulation were weighed using an electronic balance (Sartorius, 2434, Germany) and mean and relative standard deviations of the weight were determined based on an official method [16].

Hardness, Thickness and friability

The diametrical crushing strength test was performed on 10 tablets from each formulation. 10 tablets were tested using an Erweka TB24 (Germany) hardness tester. A slide calipers was used to measure the thickness for 5 tablets.

For each formulation, the friability of 20 tablets was determined using a Roche type friabilitor (Erweka, Germany). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation [16]:

$\% F = (W_1-W_2)/W_1 \times 100$ ---------- (1)

Disintegration time

Disintegration times of the prepared tablets were measured in 900 ml of purified water with disc at 37 ^{0}C, using Erweka TAR series tester. Disintegration times of 6 individual tablets were recorded.

Drug content determination

Drug content for Acetaminophen was carried out by measuring the absorbance of the sample at 257 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard Acetaminophen in the same medium by taking 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken, suitably dissolved in pH 5.8 phosphate buffer, making dilution and analyzed and carried out in triplicate and mean was taken.

***In vitro* dissolution study of tablets**

Dissolution studies were conducted using a tablet dissolution tester (Dissolution Tester [US Pharmacopeia] VEEGO VDA 8 DR, Germany), type II (paddle method), in 900 ml of pH 5.8 phosphate buffer at 37.5°C ± 0.5°C. The stirring speed was set at 50 rpm. At predetermined time intervals, a 5 ml sample was withdrawn and replaced with fresh dissolution medium. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for Acetaminophen by UV spectrophotometer (Shimadzu 1240, UV visible spectrophotometer, Japan). The amounts of drug present in the samples were calculated with the help of straight-line equation obtained from the calibration curves for respective drug. The mean of six tablets from each formulation was used in data analysis. The dissolution study was continued for 45 minutes (interval 5, 10, 15, 20, 25, 30, 35, 40, 45, minutes) to get a simulated picture of the drug release in the in-vivo condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. Time required for 25, 50 and 80% of the drug release (T_{25}%, T_{50}%, T_{80}%) was used to compare the dissolution results.

Statistical Analysis:

A one way analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate and comparison of Successive dissolution time (T_{50}%, T_{80}%) of all formulations. A confidence limit of $P < .05$ was fixed and the theoretical calculated values of *F (Fcrit and Fcal)* were compared for the interpretation of results. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA).

RESULTS

Physical Evaluation of tablets

The tablets of the proposed formulations (A1 to A6) were evaluated for hardness, weight variation, thickness, friability, disintegration, % LOD of granules and drug content showed in the Table 2.

The thickness (mean ± SD, within 0.4, n=5) of the tablets were ranged from 5.21 to 5.26 mm. The hardness (mean ± SD, within 0.4, n=10) and percentage friability (< 1%) of the tablets of all batches ranged from 17.3 to 18 kgf and 0.09 to 0.11 %, respectively. The average percentage weight deviation of 10 tablets of each formula was less than ± 5%. Drug content (mean value ± SD within 0.9) among different batches of tablets ranged from 248.57 mg to 252.49 mg. Disintegration time was ranged from 5.9 to 12.11 minutes.

In vitro dissolution studies

The effect of mode of addition of different types of disintegrants (crospovidone, sodium starch glycolate and sodium carboxymethylcellulose) of acetaminophen release is shown in Figure 1.

The formulations A1 and A2 containing crospovidone, A3 and A4 containing sodium starch glycolate, A5 and A6, containing sodium carboxymethylcellulose intragranularly (IG) and extragranularly (EG) respectively and their % drug release(Mean ±SD within 0.9, n=6) after 45 minutes is 96%, 96.5 %, 77.95 %, 83.5%, 62.5% and 65.0%. The formulations M1, M2 and M3 from market sample and their % release are 95.4%, 80.3% and 82.0%.

The rate of drug release was found to be related to the types of disintegrants present in the tablets. The release rate was significantly dependent on the types of the disintegrants. A statistically significant decrease *(P <.05, Fcrit (2, 15) = 3.68 and Fcal = 2103.71)* at the end of 5 minutes, *(P <.05, Fcrit (2, 15) = 3.68 and Fcal = 956.19)* at the end of 30 minutes, *(P <.05, Fcrit (2, 15) = 3.68 and Fcal = 205.46)* at the end of 45 minutes was observed % drug release in the three types of formulations A1& A2, A3 & A4 and A5 & A6. No significant difference *(P >.05, Fcrit (1, 10) = 4.69 and Fcal = 3.71, Fcrit > Fcal)* at the end of 45 minutes was observed between the formulation A1 and A2. Significant difference was also observed between A3 & A4 *(P <.05, Fcrit (1, 10) = 4.69 and Fcal = 124.55)* and A5 & A6*(P <.05, Fcrit (1, 10) = 4.69 and Fcal = 35.22) at the end of 45 minutes.*

Successive dissolution time ($T_{25\%,}$ $T_{50\%,}$ $T_{80\%}$ values), time required for 25%, 50% and 80% drug release from all the designed formulations are shown in figure 2.

Time required for 50% drug release, $T_{50\%}$ values increased significantly *P < .05, Fcrit (2, 15) = 3.68 and Fcal = 435.08)* observed in the three types of formulations A1& A2, A3 & A4 and A5 & A6, containing crospovidone, sodium starch glycolate and sodium carboxymethylcellulose, IG and EG respectively.

Time required for 80% drug release $T_{80\%}$ values also increased significantly *P < .05, Fcrit (2, 15) = 3.68 and Fcal = 604.88)* observed in the three types of formulations A1& A2, A3 & A4 and A5 & A6 containing crospovidone, sodium starch glycolate and sodium carboxymethylcellulose, IG and EG respectively.

Successive dissolution time ($T_{25\%,}$ $T_{50\%,}$ $T_{80\%}$ values), time required for 25%, 50% and 80% drug release from all the designed formulations are shown in the tables 3.

The formulations A1 and A2 containing crospovidone intragranurly and extragranurly respectively showed % drug release (Mean ±SD within 0.9, n=6) after 5 minutes are 55.5% and 56.3% respectively wherein three different branded market samples M1, M2 and M3 showed the releases are 30.1%, 27.8%, 20.1% respectively. After 30 and 45 minutes minutes these formulations (A1, A2, M1, M2, and M3) showed 86.0%, 86.0%, 80.2%, 76.0%, and 79.4% respectively.

Among the all formulations also with market formulations, A1 and A2 containing crospovidone showed highest percent of drug release showed in figure 3.

Successive drug release ($T_{25\%,}$ $T_{50\%,}$ $T_{80\%}$ values$_{),}$ time required for 25%, 50% and 80% release from the designed optimized formulas also showed lowest values than other formulations. $T_{25\%,}$ $T_{50\%,}$ $T_{80\%}$ values from the optimized formulas (A1, A2) are 0.089, 2.203, 19.430 and 0.068, 1.932, 18.647 minutes respectively in which market samples, three different brands (M1, M2, M3) showed 2.993, 11.731, 29.617, 3.648, 14.496, 36.944, 6.260, 17.642, 35.617 minutes respectively showed in the figure 4.

DISCUSSION:

Physical Evaluation of Acetaminophen tablets

The present study was carried out to formulate immediate release tablets using different disintegrants for Acetaminophen tablets. The drug content of all formulations was between 99.43 and 100.01 %, indicating the presence of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed acceptable hardness and friability, indicating suitable for wet granulation method.

The disintegration time was dependent on the type of disintegrants used. The disintegration times of Acetaminophen tablets, where the disintegrants were added EG, IG showed that tablets prepared with CP showed little difference in disintegration times, while the disintegration times increased for tablets containing Na-CMC and SSG, when these were added IG as well as EG (Table 2). The disintegration times of tablets containing Na-CMC and SSG IG increased disintegration time (DT) compared to the respective disintegration time of the tablets containing these disintegrants, added EG. Na-CMC showed highest DT.

Crospovidone are densely cross-linked homopolymers of N-vinyl 2-pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration [17].

Visually, tablets formulated with Crospovidone could be seen to rapidly disintegrate into more or less uniform fine particles; while tablets formulated with Na-CMC and Sodium starch glycolate appeared to disintegrate much more slowly into more or less uniform coarser particles. Tablets containing Na-CMC and Sodium starch glycolate seemed to swell immediately. This was in accordance with earlier findings where tablets prepared with Croscarmellose sodium, Na-CMC and Sodium starch glycolate showed tremendous swelling before disintegration [18-20].

The results showed that both the IG and EG of CP achieved much faster dissolution of acetaminophen when compared to Na-CMC and sodium starch glycolate. The release of acetaminophen from tablets containing CP was little affected by the mode of addition (Intragranular, Extragranular). However, in case of SSG and Na-CMC extra granular addition seemed to be preferable. From the formulation it is clear that the formulation A1 and A2 containing same amount of crospovidone IG and Crospovidone EG and there is no significant difference of drug release. SSG and CP generally swell rapidly and the extent of swelling of CP is more than that of SSG, which might have resulted in marginally slower disintegration time of tablets prepared with CP. In the case of sodium carboxymethylcellulose provided very poor release especially intragranularly and also large T_{50} and T_{80} values, indicating that sodium carboxymethylcellulose are well known binder when used intragranularly but lose their disintegrant property after wet granulation [21].

Two formulations (A1 and A2) showed highest release and time required for 50% and 80% drug release ($T_{50\%,\ \&}$ $T_{80\%}$ values) is low (below 3 minutes and blew 20 minutes), indicating very faster dissolution wherein market samples (M_1, M_2, M_3) showed relatively decreasing drug release and more time required for 50% and 80% drug release than the prepared formulations.

CONCLUSIONS

The study demonstrated that out of the disintegrants studied crospovidone was superior to the other disintegrants for the drug studied and in general the extragranular incorporation seemed to favour the dissolution. Acetaminophen tablet formulation containing crospovidone showed fasted rate of dissolution both intragranularly and extragranularly wherein the formulations containing sodium starch glycolate and sodium carboxymethylcellulose with intragranularly showed significant decreasing the drug release than extragranularly.

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Table 1. Formulation Acetaminophen immediate release tablets containing different types of disintegrants

Code	Acetaminophen	CP (IG)	CP (EG)	SSG (IG)	SSG (EG)	Na CMC (IG)	Na CMC (EG)	Avicel pH 101
		(mg/tablet)						
A1	250	14	------	------	--------	-------	-------	41
A2	250	--------	14	------	--------	-------	-------	41
A3	250	--------	------	14	--------	-------	-------	41
A4	250	-------	------	------	14	-------	-------	41
A5	250	-------	------	------	-------	14	-------	41
A6	250	-------	------	------	-------	-------	14	41

Each formulation also contains lactose 32 mg, Pov-K30 11 mg, magnesium stearate 3.5 mg, aerosil 2mg and Talc 3.5 mg. Compression weight of each formulation was 350 mg. CP(crospovidone), SSG(sodium starch glycolate), Na-CMC(sodium carboxymethylcellulose), IG(intragranularly), EG(extragranularly)

Table: 2. Evaluation of physical properties of tablets containing Acetaminophen

Physical Properties	Formulation Code					
	A1	**A2**	**A3**	**A4**	**A5**	**A6**
Hardness (kgf)	17.7 ±0.2	17.5 ±0.3	17.9 ±0.2	17.3 ±0.4	18.0 ±0.1	17.3 ±0.2
Thikness (mm)	5.23 ±0.1	5.22 ±0.2	5.22 ±0.4	5.21 ±0.4	5.21 ±0.2	5.26 ±0.3
Friability (%)	0.09	0.53	0.09	0.12	.09	.11
Weight variation	350.6 ±0.9	349.19 ±1.5	348.99 ±1.2	349.85 ±0.99	353.01 ±2.05	350.98 ±1.8
DT(min)	4.07	3.93	5.9	6.2	12.11	10.22
LOD (%)	3.52	3.22	2.93	3.00	3.09	3.25
Content (%)	251.56 ±0.9	248.57 ±0.5	249.88 ±0.8	249.25 ±0.9	252.49 ±0.7	251.66 ±0.6

Table 3: Successive fractional dissolution time of Acetaminophen tablets formulated with different disintegrating agents

Formulation	$T_{25\%\ (Min)}$	$T_{50\%\ (Min)}$	$T_{80\%\ (Min)}$
A1	0.089	2.203	19.430
A2	0.068	1.932	18.647
A3	3.940	19.656	58.447
A4	3.157	15.868	47.424
A5	8.255	30.513	74.041
A6	5.586	25.733	72.492
M1	2.993	11.731	29.617
M2	3.648	14.496	36.944
M3	6.260	17.642	35.617

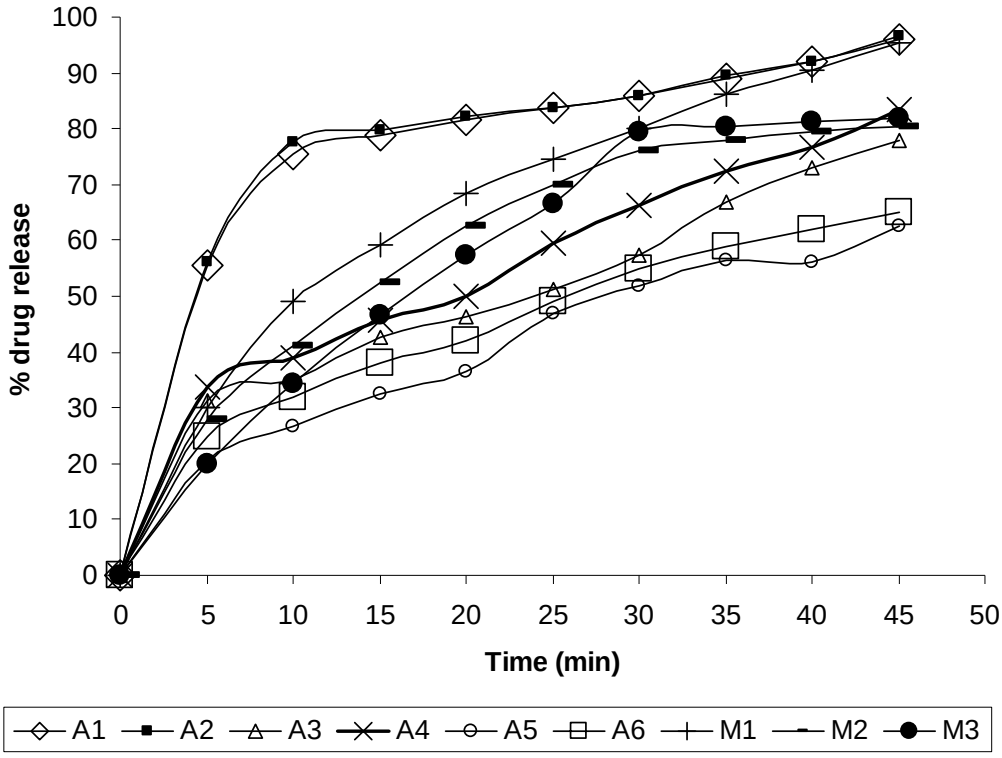

Figure1: Effect of mode of addition of disintegrants on release of Acetaminophen tablets prepared using different types of disintegrants and comparison with three different branded market samples

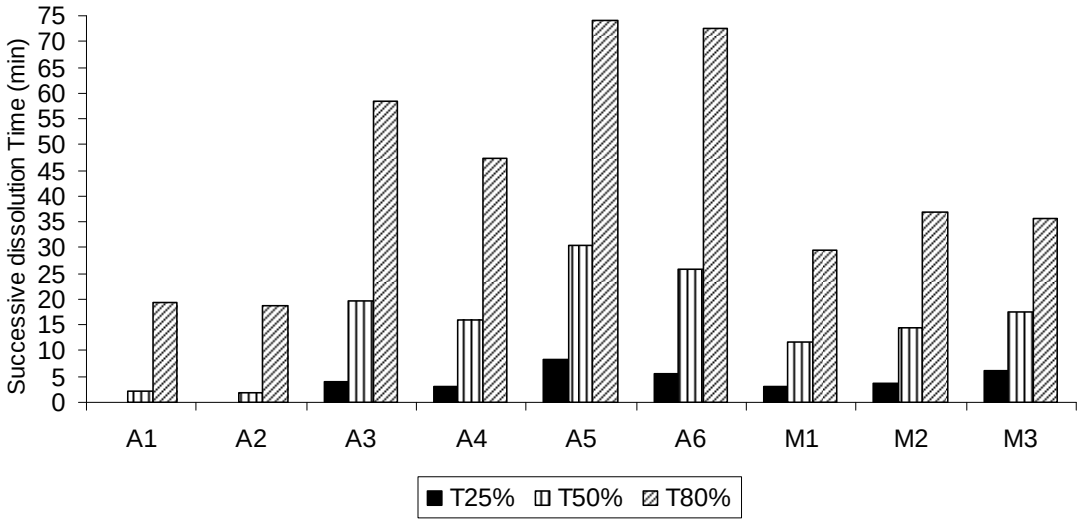

Figure 2: Successive dissolution time [$T_{25\%}$, $T_{50\%}$, $T_{80\%}$] of different Acetaminophen formulations containing various types of disintegrants

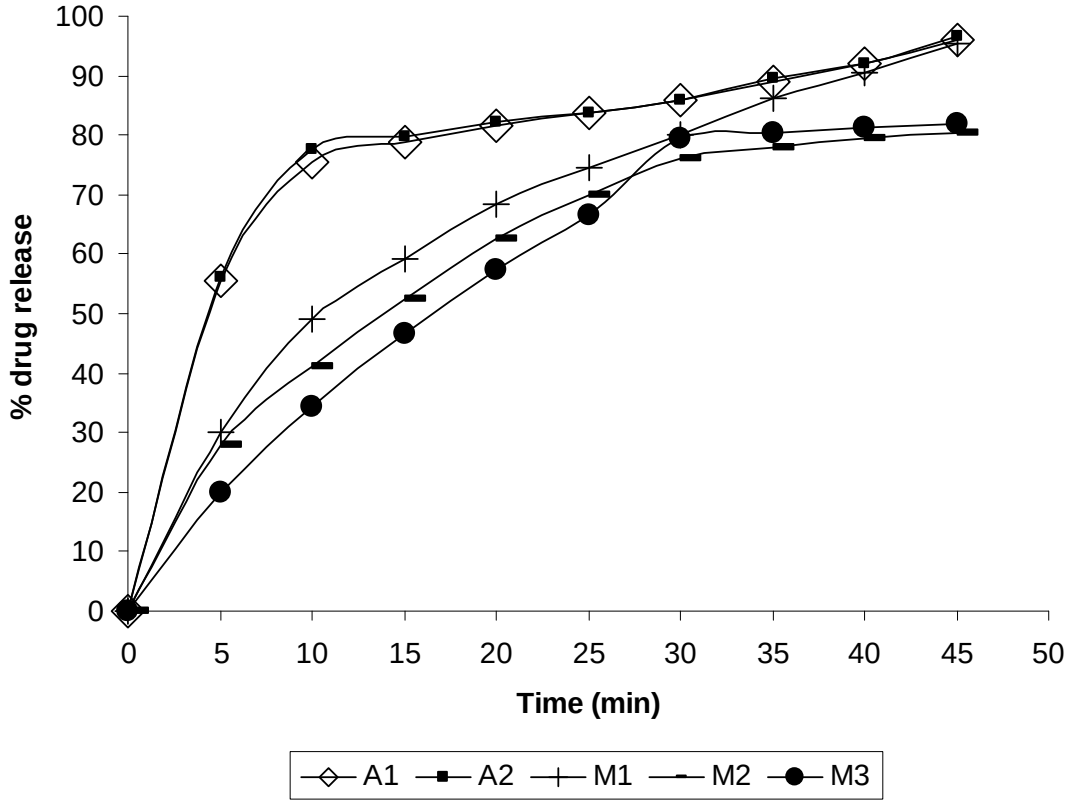

Figure 3: Comparison of % drug release of optimized formulations, A1 and A2 containing crosspovidone intragranularly and extragranularly respectively for acetaminophen with three different branded market samples M1, M2 and M3.

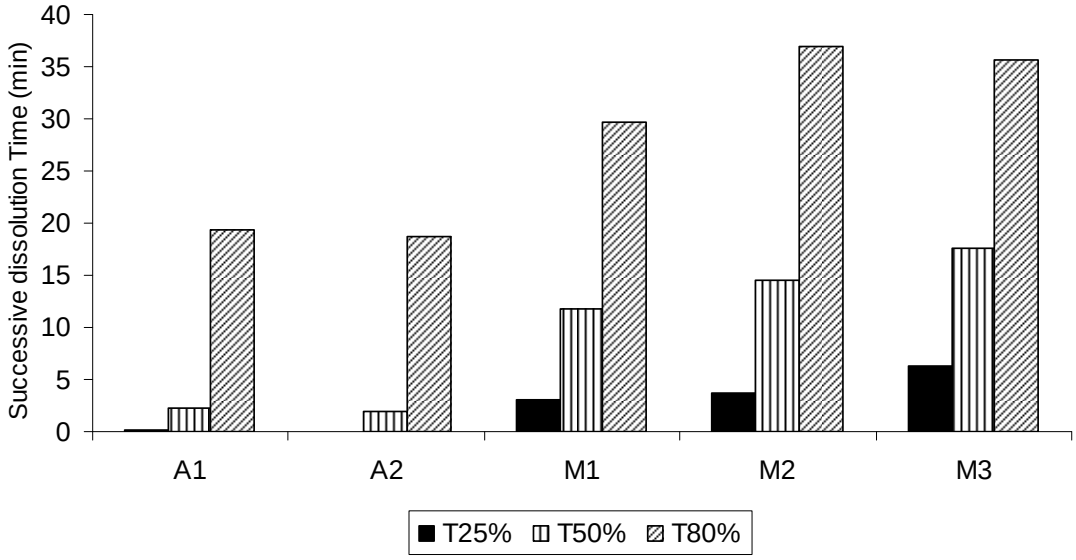

Figure 4: Comparison of Successive dissolution time [$T_{25\%}$, $T_{50\%}$, $T_{80\%}$] of optimized formulations, A1 and A2, containing crosspovidone intragranularly and extragranularly respectively for Acetoaminophen with three different branded market samples M1, M2 and M3.