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DISSOLUTION INCOMPATIBILITY OF PARACETAMOL AS A SILENT DISSOLUTION RETARDENT OF CONCOMITANTLY ADMINISTERED DRUGS

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ABSTRACT

High strength tablets containing 500 mg or more active ingredients could affect the dissolution of concomitantly administered drugs. Dissolution of ten generic solid dosage forms was determined in the presence of sodium bicarbonate and paracetamol, 500 – 2250 mg. In a total of 111 dissolution tests 41 failed (37%) to meet the criteria. Where paracetamol was present 36 out of 50 end points failed (72%) with an extreme case in diltiazem tablets with 0% dissolution. Since longest test end points with failures mostly range from 60 – 90 minutes it is advisable to administer paracetamol 1.5 hours after other drugs in order to avoid potential pharmacokinetic disturbances.

Key words: Dissolution incompatibility, paracetamol, sodium bicarbonate, diltiazem.

INTRODUCTION

The influence on dissolution of a given drug in the presence of a second drug had not been attempted so far. It is all too well known in the study of physico chemical incompatibilities in pharmacy that a dissolved solute could be thrown out of solution as a result of common-ion effect, precipitation or a less soluble complex formation following the addition of a second substance [1]. The main objective of the investigation was to determine the possible retardation of dissolution of solid dosage forms in the presence of a high strength second drug. The performance of ten products according to the compendia dissolution tests, with and without the high strength drug were compared for the purpose. The compendia dissolution tests were made use as a research tool for this purpose. A tablet with an unusually high strength of active ingredients containing paracetamol 500 mg + sodium bicarbonate 625 mg is currently being marketed. Although sodium bicarbonate is claimed as an excipient in the formulation there is nothing that could prevent it from exerting its pharmacological and physico-chemical effects. Some of these include gastric acid neutralization, effervescence, acid re-bounce, systemic alkalization, hypernatreamia, certain chemical reactions as well as possible shifts in pH of the gastro intestinal fluids [2]. Given the nature of this chemical it brings about most of these actions almost instantaneously. The situation is more acute since the practice is to administer two tablets at a time that amounts to paracetamol (acetaminophen) 1000 mg and sodium bicarbonate 1250 mg totaling 2250 mg of active ingredients. Repeat daily doses could aggravate these untoward effects. Tear off lines in the blister packs are for two tablets encouraging the two tablet prescription practice. Such large doses look all

the more heroic when contrasted with the strength of one of the test items Trifluoperazine Tablets 5 mg.
It was not anticipated that paracetamol may have any influence on the dissolution of the test items. It is a weak acid with a pKa of 9.51. The molecule has weak negative charges surrounding the two oxygen atoms and the N atom of the amino group. To predict alteration to dissolution of a second drug based on such properties of the first drug is not easy. Therefore an experiment based project was undertaken. In majority of instances where dissolution had been reduced, it was evident that the failures were in the presence of paracetamol. In certain developed countries the 'Regular Strength' of Paracetamol (Acetaminophen) Tablets is 325 mg and 'Extra Strength' is referred to the 500 mg tablets.

In the drug discovery tradition, as undergraduates we were taught that as a 'rule of thumb' no agent is considered favorably as a prospective drug if the effective dose is found to be in excess of 500 mg unless the screening is for an incurable disease. This is partly because the size of the oral dosage form becomes unacceptably large and difficult to swallow. For instance in the early 1940s para-aminosalisylic acid (PAS) was administered for tuberculosis thrice a day each dose consisting of 4.0 g of granules packed in sachets [3]. Contents have to be dispersed in a suitable fluid such as fruit juices and swallowed. It was a life threatening disease at that time. It has made a comeback due to emergence of resistance strains.

The dissolution tests in the official compendia are designed to provide for workable uniform test procedures for the industry. It reflects the solubility mechanisms and the absorption windows of the given drug in the gastro-intestinal tract to a reasonable extent. The current outlook of the dissolution test is to provide for a probable *in vivo* performance of the drug through dissolution tests [4]. Among the ten selected dosage forms the dissolution test specifications varied with respect to the medium, apparatus, revolutions per minute, dissolution test end points and the percent dissolution to be achieved at each test end point (Table 1). There were dissolution end points varying between 15 – 180 minutes specified for the ten dosage forms selected for the tests, none of which are sustained release preparations.

It was felt that the presence of a large amount of sodium bicarbonate, paracetamol or their combination may adversely affect concomitantly administered dosage forms that would otherwise meet the dissolution test requirements. In a similar study dissolution of paracetamol and Ibuprofen in the presence of a range of excipients had been determined and it was found that alkalizing excipients may alter the rate and extent of dissolution of these drugs [5]. Another concern of the present study was that a lowered dissolution rate of a concomitantly administered drug may in turn result in poor bioavailability of that drug.

As a quality control measure standard dissolution tests for all test dosages were performed according to The British Pharmacopoeia 2015 or The United States Pharmacopoeia 32nd edition to ensure that the products meet the specifications (Tables 2-11, step 1). In order to mimic the concomitant administration of the second high strength drug, each test tablet was subjected to dissolution tests in the presence of the suspected offending agents, sodium bicarbonate, paracetamol + sodium bicarbonate tablet(s) or the paracetamol tablet(s). The dissolution tests were performed mainly in the compendia specified media for the given drug with the exception in steps 4 and 5 where de-ionized water was used as indicated in tables 2- 11. Dissolution percentages are quoted in the text without decimal values for convenience.

MATERIALS AND METHODS

Ten well established generic solid dosage forms produced by the State Pharmaceuticals Manufacturing Corporation, No. 11 Sir John Kotalawala Mawatha, Kandawale Estate, Ratmalana, Sri Lanka were selected for the study. Nine immediate release generic tablets and one capsule consisting of carbamazepine, cloxacillin sodium, diclofenac sodium (delayed release), diltiazem hydrochloride, gliclazide, metformin hydrochloride, phenoxymethylpenicillin potassium, propranalol hydrochloride, trifluoperazine hydrochloride and verapamil hydrochloride were selected for the concomitant dissolution tests. They represent acid salts, alkali salts and unconverted original drug molecules.

Prospective dissolution interfering items selected for the study were the brand PANADOL tablets containing pracetamol 500 mg manufactured by SmithKline Beecham (Pvt) Ltd., 121, Galle Road, Kaldemulla, Moratuwa, Sri Lanka and the brand PANADOL ACTIFAST tablets containing paracetamol 500 mg + sodium bicarbonate 625 mg manufactured by GlaxoSmithKline Dungarvan Ltd., Co. Waterford, Ireland. Pharmacopoeia grade sodium bicarbonate powder was the other item. Dissolution was carried out in Toyama Dissolution Tester, Model Number NTR VS3, Toyama Sangyo Co; Ltd; Osaka, Japan. Spectrophotometer used was made by Agilent

Technology, Model Number Cary8454uv-vis, Germany and the pH Meter was of the same make, Model Number 3200P, Switzerland.

For the concomitant dissolution experiments basically two types of media were used, i) mainly the compendia recommended media and ii) de-ionized water in selected tests. Under type i) at the commencement all ten dosage forms were subjected to the relevant pharmacopeia dissolution tests as a control measure for reference purpose before the study proper (Tables 2 -11, step 1). In the steps that followed in addition to the test tablet, the compendia dissolution medium were introduced with sodium bicarbonate powder 625 mg and 1250 mg (Tables 2-11, steps 2 and 3). This was followed by introducing two paracetamol + sodium bicarbonate tablets and two paracetamol tablets in to the medium at the same time as the test dosage form was introduced (Tables 2 -11, steps 6 and 7). In selected cases where there were serious shortfalls in the amount dissolved in the presence of two tablets, the tests were repeated with one tablet (Table 3, step 8, Table 5, steps 8 and 9, Table 11, step 8). As a requirement of the present study dissolution was performed up to an additional 30 minutes beyond the prescribed time in all cases.

First sodium bicarbonate powder 625 mg which is the amount found in one unit of the combination tablet was added and dissolved in the respective compendia recommended dissolution media of the test dosage forms. The dissolution tests commenced soon after with the introduction of the test dosage form. When it was realized repeatedly that with 625 mg there were no significant differences between the dissolution percentages with that of the officially specified values (Tables 2 -11, steps 1 and 2), this step was abandoned for the rest of the test dosage forms indicated in the tables by N/A where applicable. Similar tests were repeated for all dosage forms using 1250 mg of sodium bicarbonate powder, the amount found in two units of the combination tablets anticipating a change in dissolution with the higher strength.

In the case of dissolution tests in the presence of one or two paracetamol + sodium bicarbonate tablet(s) or one or two paracetamol tablet(s), they were added to the respective media at the same time as the test tablets were added at the commencement of the tests. Since in most instances compendia dissolution media had a buffer system or pH adjustment, the dissolution tests were thereafter followed with non- compendia medium de-ionized water under type ii) tests. The first test was with plain de-ionized water as a measure of dissolution of the tablets without a pH adjustment in which all other specifications were kept same as that of the compendia for the given tablet (Tables 2 -11, step 4). A second test with de-ionized water + sodium bicarbonate powder 1250 mg was performed to find out if there are changes to dissolution due to the presence of this salt (Tables 2 -11, step 5). Sodium bicarbonate 1250 mg is to represent this ingredient found in two units of the combination tablet.

During the dissolution tests the initial and the final pH values at the end of the official test end points were monitored and all pH shifts in excess of ± 1 were tabulated (Table 12).

In the analysis for the amount dissolved from the test dosage forms, the absorbance due to dissolved sodium bicarbonate and paracetamol had to be eliminated. An independent additional dissolution test was introduced in all steps for this purpose. Here the dissolution of sodium bicarbonate 625 mg, 1250 mg, one or two units each of paracetamol + sodium bicarbonate tablet(s) or paracetamol tablet(s) as appropriate were carried out without the test tablet. The same specific compendia recommended media and conditions for the test dosages were used in these tests. An aliquot similar to the one drawn at the compendia test end point was also drawn from the independent test at the same time point. This was used as the blank solution for the zero adjustment of the spectrophotometer. Standard solutions for the analysis were prepared using the reference standards of the pharmacopoeia or the respective secondary standards.

RESULTS AND DISCUSSION

The dissolution results of the ten test dosage forms were tabulated including the results of the additional 30 minute following the official end points. Only the test drug was present in steps 1 and 4. The cut off for the additional reading was considered to be the same percentage dissolution as that of the official end point. Carbamazepine Tablets and Diltiazem Hydrochloride Tablets had two official end points. In the case of Diclofenac Sodium Delayed Release Tablets the acid medium results were excluded as they all had zero dissolution as expected. The percentage dissolution values initially arrived at was the average of six determinations but were later reduced to three determinations considering the exceptional uniformity of the individual dissolution values, where the standard deviation of the values are mostly less than ± 5%.

Tests with sodium bicarbonate in compendia specified dissolution media: Under the scheme of analysis the initial step for each test item was conducted under the compendia specified regular dissolution tests. In these tests the end points of all the ten dosage forms were found to comply with the official requirements (Tables 2 -11, step 1). This ensured that the selected batches were of acceptable quality with regard to dissolution and could be taken as reference points for the tests to be followed. All these batches were approved earlier and released in to the market by the manufacturer.

This was followed by two more steps using compendia specified dissolution media where in addition to the test dosage form, 625 mg and 1250 mg of sodium bicarbonate were added for all test tablets (Table 2 -11, steps 2 and 3). All the test end points were found to comply and there were no differences in the results to the previous step 1 tests without sodium bicarbonate. For a given tablet the results of all these three steps yielded nearly the same values. This may probably be due to effective buffer systems of these media preventing any influence due to sodium bicarbonate. However there was no buffer system in the case of carbamazepine that has wetting agent sodium lauryl sulphate, cloxacillin and diltiazem where the compendia specified media were plain De-ionized Water (Table 1).

Incidentally the pH values at the official test end points of all test items in the steps 1, 2 and 3 were found to remain nearly the same as the initial pH values. Hence it can be said that two strengths of sodium bicarbonate employed had no effect on the pH or the dissolution of any of the test dosage forms in the compendia recommended media.

Tests replacing compendia specified dissolution media with de- ionized water: Since all the above test end points in the compendia prescribed buffered media even in the presence of sodium bicarbonate complied with the dissolution criteria two more dissolution test series were performed in plain de-ionized water and de- ionized water + sodium bicarbonate powder 1250 mg without the buffer systems (Tables 2 – 11, steps 4 and 5). The tests in plain de-ionized water will give an indication of the inherent dissolution of the test dosage forms. Dissolution failures in de-ionized water were observed for carbamazepine, gliclazide and trifluoperazine tablets (Tables 2, 6 and 10, step 4). Failures were again recorded in de-ionized water + sodium bicarbonate media in step 5 for carbamazepine and trifluoperazine whereas gliclazide complied. This indicates that the alkaline medium favored dissolution of gliclazide tablets. It must be noted that in these tests, for cloxacillin and diltiazem the standard compendia specified medium is also de-ionized water. Therefore test results in the tables 3 and 5, step 1 were substituted in step 4 of the same tables for these two products.

Tests in the presence of paracetamol 1000 mg in compendia specified dissolution media: In the step that followed dissolution was carried out in the presence of two paracetamol+ sodium bicarbonate tablets introduced in to the dissolution vessel at the same time as the test dosage form. This was followed by a similar test with two units of paracetamol tablets alongside the test tablet (Tables 2 – 11, steps 6 and 7). Under both these steps it can be seen that in all of the tested tablets other than carbamazepine, diclofenac and metformin, the dissolution end points failed to meet the specified values by large margins. The values achieved were mostly about 1/3rd of the required dissolution percentages. In an extreme case there was absolute resistance down to 0% dissolution in the case of diltiazem.

Since the tests carried out in the presence of sodium bicarbonate powder had no effect, the offending agent responsible for reduced dissolution should be paracetamol. However all the test end points for carbamazepine, diclofenac and metformin had passed the tests despite the presence of paracetamol.

For trifluoperazine in the presence of two paracetamol tablets the dissolution has retarded to nearly 1/3rd of the amount compared to the results in the standard compendia test (Table 10, steps 1 and 7). In the presence of two paracetamol + sodium bicarbonate tablets the above values have been reduced further by over another 50% (Table 10, step 6). Here it is likely that sodium bicarbonate have liberated the less soluble trifluoperazine base from the hydrochloride salt. Overall these results indicate the dissolution retarding effect of paracetamol on trifluoperazine.

Selected additional tests with paracetamol 500 mg: Some of the test dosage forms that had drastically reduced dissolution in the above two steps with two tablets were subjected to an additional test with one tablet. The tests included a single tablet of paracetamol + sodium bicarbonate in the case of cloxacillin and diltiazem and a single tablet of paracetamol in the case of diltiazem and verapamil. This was to find out if half the amount of paracetamol in previous tests would still reduce the dissolution rate. In all these additional tests too there were a marked drop in the dissolution percentages

with values ranging between 0% - 32% (Tables 3, 5 and 11, steps 8 and 9). These tests further confirmed that it was paracetamol that adversely affected the dissolution.

Glyclazide tablets display typical effects of the two concomitantly administered drugs: In the case of gliclazide tablets it can be clearly seen that sodium bicarbonate has a tendency to increase dissolution and that paracetamol tends to decrease dissolution even in the presence of sodium bicarbonate. According to table 6, steps 4 and 5, poor dissolution in plain de-ionized water (46%, 56%) had been improved by nearly twice the value to over 90% in the presence of sodium bicarbonate. However in the presence of two paracetamol tablets in the compendia specified medium, the dissolution values have been reduced (36%, 42%) to less than 50% of the values in compendia specified media of over 95% (Table 6, items 1 and 7). With two paracetamol + sodium bicarbonate tablets, the dissolution values in the compendia specified medium (Table 6, step 6) are substantially less (53%, 60%) than the near 100% dissolution in same media for the three test series without paracetamol (Table 6, steps 1, 2 and 3). However the above values were more than those in the presence of two paracetamol tablets. Accordingly the gliclazide dissolution pattern can be summed up to say that the presence of sodium bicarbonate tends to improve the dissolution and the presence of paracetamol tends to reduce the dissolution even in the presence of sodium bicarbonate. This is an example of the influence of paracetamol in retarding the dissolution of a second drug in an environment that otherwise promote dissolution.

Despite many failures noted above, in the case of carbamazepine, diclofenac and metformin the presence of paracetamol had no effect on dissolution.
It was also found that with the 30 minutes of extended stirring, dissolution still failed to comply in all cases of failure with the marginal exception of carbamazepine in de-ionized water as the medium (Table 2, step 4). It may be said that the properties of the interfering chemicals is the overriding factor in the changes to dissolution compared to the time factor.

Zero adjustment apart in determining per cent dissolution, it can be assumed that the presence of paracetamol had not interfered with the absorption values since its absorption maxima 257 nm is different to most of the active ingredients. The nearest exceptions are cloxacillin also 257 nm and trifluorperazine 255 nm, furthest being propanalol at 289 nm.

The following can be identified with regard to the pH values. In majority of cases pH changes at the end of the tests have been resisted to less than ± 1%. Those with over a shift of ±1.0 are listed in Table 12 and all of these had paracetamol + sodium bicarbonate tablets except in the case of carbamazepine. The medium for verapamil was a 0.01 N hydrochloric acid solution. In other four cases the dissolution medium had been plain de-ionized water. However carbamazepine had 1% sodium lauryl sulfate intended to function as a wetting agent. Except in the case of verapamil the pH had been shifted from acidic to alkaline range.

CONCLUSION

Although the project was undertaken assuming that the probable offending ingredient would be sodium bicarbonate this was not to be. Poor dissolution with marginal failures to meet targets was noted in two items carbamazepine and trifluoperazine when the medium was plain de-ionized water. Even with the addition of the sodium bicarbonate, nearly the same failed reduction in dissolution has taken place (Tables 2 and 10, steps 4 and 5). Lack of dissolution retarding influence of this salt is further confirmed by the fact that in gliclazide, the failed dissolution in plain de-ionized water improved and complied in the presence of the salt (Table 6, steps 4 and 5). The amphoteric nature of sodium bicarbonate may be responsible for this lack of influence in altering the dissolution in majority of the tablets to the extent that was anticipated.

An interesting finding is that when the medium was the compendia recommended one, in all tests with or without sodium bicarbonate 625 mg or 1250 mg, the dissolution results complied. For the ten test dosage forms, all of the dissolution end point values for a given tablet were nearly the same in all of the three test series (Tables 2 -11, steps 1, 2 and 3). This again proves that sodium bicarbonate alone to a large extent does not influence dissolution to any substantial degree under the test conditions of the study.

In contrast, in the presence of either strength of 500 mg or 1000 mg of paracetamol with or without sodium bicarbonate led to adverse failures in dissolution as seen in all tables in steps 6- 9 except in the case of carbamazepine, diclofenac and metformin. A close examination of the diverse molecular structures of the ten active ingredients involved in interaction with paracetamol may provide a clue as to the factors that may have contributed to

the dissolution failures. Popular literature confines discussions only on single ingredient solubility [6].

Regarding the extended 3.5 hours, the dissolution achieved for diltiazem in the absence of paracetamol was over 90% (Table 5, steps 1- 5) whereas in standard media in the presence of paracetamol the dissolution range is from 14% to 32% (Table 5, steps 6 - 9). A striking finding for diltiazem is that in the presence of paracetamol, as much as four test end points showed 0% dissolution two of which are at the compendia end points at 3 hours. Dissolution at the 3 hour end points in all cases in the absence of paracetamol is also over 90%. The specified value for the first end point is not more than 60% dissolution in 30 minutes. However in the presence of paracetamol, the dissolution values achieved 0% – 6% is nowhere near the cut off value. This is not in keeping with the intended dose dumping prevention measure of this test end point. Instead it conveys an extreme resistance to dissolution of diltiazem.

It is not known how many other critical drugs, immediate or sustained release may be impacted in a similar manner in the presence of paracetamol. There may be other tablets containing or prescribed in strengths 500 mg or higher which may affect the dissolution of a second drug in the same adverse manner as paracetamol. Many drugs have poor solubility in the original form before being converted to salt forms. It is likely that high strength tablets with good solubility may have a deterrent effect on the dissolution of low strength tablets. Any solid oral dosage form whose dissolution is reduced drastically even at the end of 3.5 hours is bound to affect the bioavailability of that drug. In the light of these findings, the wide spread use of paracetamol as well as its repeat administration may have contributed to unforeseen consequences to the concomitantly administered drugs. These repercussions are yet to be realized.

In cases where paracetamol was present in the medium dissolution rates have been reduced in majority of the cases amounting to failures in 72% of the tests. This is a new finding that argues strongly against concomitant administration of a second drug with paracetamol. Since the dissolution failure end points in this study mostly cover a period of up to 75 – 90 minutes it can be recommended that paracetamol should be administered at least 1.5 hours after oral administration of any other solid oral dosage form.

It is too early to claim whether the active ingredients of liquid dosage forms will be thrown out of the solution by a similar mechanism that reduces dissolution as seen in the present study. Studies are required to establish if sustained release formulations too are affected by dissolution incompatibilities. These *in vitro* dissolution dynamics cannot be applied wholesale to *in vivo* environment where the dissolved drug begins to get absorbed after administration modifying the two settings. It will be an interesting study to see how the dissolution of a second drug is affected in the presence of paracetamol when tested in three pH values 1.2, 4.5 and 6.8 recommended by the World Health Organization for bio-waiver under biopharmaceutical classification system. Bioavailability studies of the dissolution affected drugs in the presence of paracetamol have to be carried out by concomitant administration of both the drugs in order to gauge the seriousness of this finding. The present study has identified greater use for dissolution tests promoting it from a mere quality control test to that of a research tool.

It is evident that the pH values have remained largely unaffected in most dissolution tests in this study except in few instances where a shift of over ±1 had been observed. (Table12). This is in sharp contrast to large margins of failures in dissolution. It may be concluded that dissolution failures of the present study is largely independent of the pH of the medium.

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Table 1: Compendia dissolution test specifications for the selected dosage forms.

Formulation	Dissolution medium (900 ml)	Appa-ratus	Dissolution period	RPM	Standard percent dissolution
Carbamazepine Tablets BP 200 mg	DI water containing 1% sodium lauryl sulphate	2	15 mts 60 mts	75	50%-65% NLT 75%
Cloxacillin Sodium Capsules BP 250 mg	DI water	1	30 mts	100	NLT 80%
Diclofenac Sodium Delayed Release Tablets USP 50 mg	0.1 N HCl	2	2 hours	50	N/A
	Phosphate buffer pH 6.8	2	45 mts	50	NLT 75%
Diltiazem HCl Tablets USP 60 mg	DI water	2	30 mts 3 hours	75	NMT 60% NLT 75%
Gliclazide Tablets BP 80 mg	Phosphate buffer pH 7.4	2	45 mts	100	NLT 70%
Metformin HCl Tablets BP 500 mg	Potassium dihydrogen orthophosphate 0.68% w/v pH 6.8	1	45 mts	100	NLT 70%
Phenoxymethylpenicillin Potassium Tablets BP 250 mg	Potassium dihydrogen orthophosphate 0.68% w/v pH 6.8	1	45 mts	100	NLT 70%
Propranolol HCl Tablets BP 40 mg	Dilute HCl (1in 100), (1000 ml)	1	30 mts	100	NLT 75 %
Trifluoperazine HCl Tablets BP 5 mg	0.1 N HCl	1	30 mts	50	NLT 75 %
Verapamil HCl Tablets BP 40 mg	0.01 N HCl	2	30 mts	50	NLT 75 %

Apparatus1; basket, Apparatus 2; paddle, mts; minutes, N/A; not available.

Table 2: Dissolution test results for Carbamazepine Tablets BP 200 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points		
		15 minutes	60 minutes	60 + 30 (90) minutes
1.	Medium BP (Control)	58.80 ± 1.60	83.51 ± 3.68	88.81± 3.45
2.	Medium BP + $NaHCO_3$ 625 mg	63.62 ± 4.91	86.29 ± 4.21	88.22 ± 2.71
3.	Medium BP + $NaHCO_3$ 1250 mg	64.65 ± 2.29	86.88 ± 2.89	90.44 ± 2.33
4.	De-ionized water	43.69 ± 1.47*	64.92 ± 2.39*	70.21 ± 1.45
5.	De-ionized water + $NaHCO_3$ 1250 mg	39.49 ± 0.95*	62.63 ± 2.08*	66.88 ± 2.65*
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	61.28 ± 4.39	79.75 ± 5.57	83.80 ± 14.13
7.	Medium BP + two paracetamol tablets	62.35 ± 3.63	90.47 ± 2.17	105.96 ± 12.47

*Note: Six tablets used for steps 1, 2, and 3 and three tablets for steps 4, 5, 6 and 7, dissolution prescribed at 15 minutes 50% - 65%, dissolution prescribed at 60 minutes is NLT 70%, SD; standard deviation, *Does not comply.*

Table 3: Dissolution test results for Cloxacillin Sodium Capsules BP 250 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		30 minutes	30 + 30 (60) minutes
1.	Medium BP (Control)	104.66 ± 2.99	99.86 ± 2.08
2.	Medium BP + $NaHCO_3$ 625 mg	105.82 ± 2.00	102.90 ± 2.12
3.	Medium BP + $NaHCO_3$ 1250 mg	103.88 ± 3.58	99.90 ± 3.52
4.	De-ionized water	104.66 ± 2.99	99.86 ± 2.08
5.	De-ionized water + $NaHCO_3$ 1250 mg	103.88 ± 3.58	99.90 ± 3.52
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	4.38 ± 1.17*	22.83 ± 9.51*
7.	Medium BP + two paracetamol tablets	15.62 ± 6.88*	19.55 ± 6.71*
8.	(Additional test) Medium BP + one paracetamol + sodium bicarbonate tablet	13.18 ± 4.67*	16.12 ± 4.58*

*Note: Six tablets used for steps 1, 2 and 3 and three tablets for steps 4, 5, 6, 7 and 8, dissolution prescribed at 30 minutes is NLT 80%, SD; standard deviation, *Does not comply.*

Table 4: Dissolution test results for Diclofenac Sodium Delayed Release Tablets USP 50 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		45 minutes	45 + 30 (75) minutes
1.	Medium USP (Control)	98.16 ± 3.59	97.81 ± 2.41
2.	Medium USP + $NaHCO_3$ 625 mg	N/A	N/A
3.	Medium USP + $NaHCO_3$ 1250 mg	98.35 ± 3.24	99.24 ± 1.72
4.	De-ionized water	N/A	N/A
5.	De-ionized water + $NaHCO_3$ 1250 mg	N/A	N/A
6.	Medium USP + two paracetamol + sodium bicarbonate tablets	93.82 ± 8.66	92.11 ± 4.57
7.	Medium USP + two paracetamol tablets	91.26 ± 5.19	92.85 ± 0.57

Note: Six tablets were used for all tests, dissolution prescribed at 45 minutes is NLT 75%, N/A; not available, SD; standard deviation.

Table 5: Dissolution test results for Diltiazem Hydrochloride Tablets USP 60 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points		
		30 minutes	3 hours	3.5 hours
1.	Medium USP (Control)	43.24 ± 2.25	92.75 ± 3.02	91.65 ± 3.79
2.	Medium USP + $NaHCO_3$ 625 mg	N/A	N/A	N/A
3.	Medium USP + $NaHCO_3$ 1250 mg	45.52 ± 4.89	96.76 ± 2.64	94.80 ± 2.26
4.	De-ionized water	43.24 ± 2.25	92.75 ± 3.02	91.65 ± 3.79
5.	De-ionized water + $NaHCO_3$ 1250 mg	45.52 ± 4.89	96.76 ± 2.64	94.80 ± 2.26
6.	Medium USP + two paracetamol + sodium bicarbonate tablets	0.00 ± 0.00	0.00 ± 0.00*	14.37 ± 1.69*
7.	Medium USP + two paracetamol tablets	5.05 ± 2.82	16.83 ± 2.80*	32.30 ± 1.93*
8.	(Additional test) Medium USP + one paracetamol + sodium bicarbonate tablet	0.00 ± 0.00	0.00 ± 0.00*	20.84 ± 4.04*
9.	(Additional test) Medium USP + one paracetamol tablet	6.37 ± 1.22	17.59 ± 1.68*	31.05 ± 3.14*

*Note: Six tablets used for steps 1 and 3 and three tablets for steps 4, 5, 6, 7, 8 and 9, dissolution prescribed at 30 minutes is NMT 60%, dissolution prescribed at 3 hours is NLT 75%, N/A; not available, SD; standard deviation,*does not comply.*

Table 6: Dissolution test results for Gliclazide Tablets BP 80 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		45 minutes	45 + 30 (75) minutes
1.	Medium BP (Control)	97.12 ± 1.50	95.59 ± 6.17
2.	Medium BP + $NaHCO_3$ 625 mg	91.88 ± 10.28	87.31 ± 5.99
3.	Medium BP + $NaHCO_3$ 1250 mg	115.28 ± 1.32	112.28 ± 2.79
4.	De-ionized water	46 ± 1.06*	56.56 ± 0.83*
5.	De-ionized water + $NaHCO_3$ 1250 mg	92.87 ± 2.13	96.33 ± 1.34
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	53.56 ± 19.31*	60.02 ± 20.77*
7.	Medium BP + two paracetamol tablets	36.86 ± 8.59*	42.30 ± 5.56*

*Note: Six tablets used for steps 1, 2 and 3 and three tablets for steps 4, 5, 6 and 7, dissolution prescribed at 45 minutes is NLT 70%, SD; standard deviation,*Does not comply.*

Table 7: Dissolution test results for Metformin Hydrochloride Tablets BP 500 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		45 minutes	45 + 30 (75) minutes
1.	Medium BP (Control)	110.66 ± 9.97	93.53 ± 2.01
2.	Medium BP + $NaHCO_3$ 625 mg	99.86 ± 6.28	97.89 ± 5.93
3.	Medium BP + $NaHCO_3$ 1250 mg	106.08 ± 1.96	103.77 ± 2.81
4.	De-ionized water	95.14 ± 1.61	88.44 ± 5.03
5.	De-ionized water + $NaHCO_3$ 1250 mg	105.41 ± 1.34	103.03 ± 0.79
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	99.60 ± 8.79	94.09 ± 8.25
7.	Medium BP + two paracetamol tablets	105.41 ± 2.27	99.53 ± 2.77

Note: Six tablets used for steps 1,2 and 3 and three tablets for steps 4,5,6 and 7, dissolution prescribed at 45 minutes is NLT 70%, SD; standard deviation.

Table 8: Dissolution test results for Phenoxymethylpenicillin Potassium Tablets BP 250 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		45 minutes	45 + 30 (75) minutes
1.	Medium BP (Control)	107.24 ± 1.26	104.86 ± 1.53
2.	Medium BP + $NaHCO_3$ 625 mg	110.15 ± 2.47	107.16 ± 1.55
3.	Medium BP + $NaHCO_3$ 1250 mg	99.04 ± 3.86	97.99 ± 7.22
4.	De-ionized water	107.24 ± 6.49	105.29 ± 6.68
5.	De-ionized water + $NaHCO_3$ 1250 mg	108.64 ± 0.29	105.06 ± 0.25
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	17.69 ± 3.15*	18.75 ± 3.51*
7.	Medium BP + two paracetamol tablets	17.54 ± 4.48*	23.58 ± 6.39*

*Note: Six tablets used for steps 1,2 and 3 and three tablets for steps 4,5,6 and 7, dissolution prescribed at 45 minutes is NLT 70%, SD; standard deviation,*Does not comply.*

Table 9: Dissolution test results for Propranolol Hydrochloride Tablets BP 40 mg.

Note: Six tablets used for steps 1,2 and 3 and three tablets for steps 4,5,6 and 7, dissolution prescribed at 30

Steps	Media and variants	Mean % dissolution with SD at test end points	
		30 minutes	30 + 30 (60) minutes
1.	Medium BP (Control)	103.85 ± 1.38	101.22 ± 1.74
2.	Medium BP + $NaHCO_3$ 625 mg	104.48 ± 1.58	100.83 ± 1.75
3.	Medium BP + $NaHCO_3$ 1250 mg	103.78 ± 0.85	101.03 ± 1.16
4.	De-ionized water	95.73 ± 2.05	95.68 ± 2.01
5.	De-ionized water + $NaHCO_3$ 1250 mg	101.43 ± 2.61	97.92 ± 3.19
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	20.22 ± 7.43*	21.16 ± 3.36*
7.	Medium BP + two paracetamol tablets	28.12 ± 9.89*	32.88 ± 7.03*

*(Shift line above table here) minutes is NLT 75%, SD; standard deviation,*Does not comply.*

Table 10: Dissolution test results for Trifluoperazine Hydrochloride Tablets BP 5 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		30 minutes	30 + 30 (60) minutes
1.	Medium BP (Control)	101.40 ± 1.99	98.17 ± 2.14
2.	Medium BP + $NaHCO_3$ 625 mg	N/A	N/A
3.	Medium BP + $NaHCO_3$ 1250 mg	94.85 ± 3.13	91.44 ± 2.24
4.	De-ionized water	63.38 ± 5.52*	70.29 ± 5.49*
5.	De-ionized water + $NaHCO_3$ 1250 mg	62.48 ± 4.59*	65.36 ± 5.81*
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	13.10 ± 6.05*	16.07 ± 8.76*
7.	Medium BP + two paracetamol tablets	29.63 ± 3.28*	37.89 ± 1.79*

*Note: Six tablets used for steps 1 and 3, and three tablets for steps 4, 5,6 and 7, dissolution prescribed at 30 minutes is NLT 75%, SD; standard deviation,*Does not comply.*

Table 11: Dissolution test results for Verapamil Hydrochloride Tablets BP 40 mg.

Steps	Media and variants	Mean % dissolution with SD at test end points	
		30 minutes	30 + 30 (60) minutes
1.	Medium BP (Control)	104.88 ± 3.37	90.97 ± 0.77
2.	Medium BP + $NaHCO_3$ 625 mg	95.25 ± 1.17	92.51 ± 1.46
3.	Medium BP + $NaHCO_3$ 1250 mg	95.41 ± 5.76	90.68 ± 1.09
4.	De-ionized water	96.75 ± 1.87	94.73 ± 2.72
5.	De-ionized water + $NaHCO_3$ 1250 mg	98.25 ± 2.63	95.57 ± 3.78
6.	Medium BP + two paracetamol + sodium bicarbonate tablets	14.20 ± 5.70*	7.33 ± 5.66*
7.	Medium BP + two paracetamol tablets	7.00 ± 3.09*	8.82 ± 3.64*
8.	(Additional test) Medium BP + one paracetamol tablet	5.44 ± 1.69*	7.07 ± 2.66*

*Note: Six tablets used for steps 1, 2 and 3 and three tablets for steps 4,5,6,7 and 8, dissolution prescribed at 30 minutes is NLT 75%, SD; standard deviation, *Does not comply.*

Table 12: Dissolution tests where initial to final average pH shift is more than ± 1.

Drug	Dissolution medium	Initial pH (A)	Final pH at end point (C)	pH Shift (A-C)
Carbamazepine Tablets BP 200 mg	De-ionized water	5.4	7.53	2.13
Cloxacillin Sodium Capsules BP 250 mg	Medium BP + two paracetamol + sodium bicarbonate tablets	5.4	8.33	2.93
	Medium BP + one paracetamol + sodium bicarbonate tablet	6.35	8.09	1.74
Diltiazem Hydrochloride Tablets USP 60 mg	Medium USP + two paracetamol + sodium bicarbonate tablets	6.3	8.3	2.00
Verapamil Hydrochloride Tablets BP 40 mg	Medium BP + two paracetamol + sodium bicarbonate tablets	2.3	6.4	4.1

Initial pH is media pH ready to introduce tablets. Final pH is the value at standard test end point.

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