COMPARATIVE DISSOLUTION RATE STUDIES ON NON NARCOTIC ANALGESICS

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Abstract

Five different brands of these non-narcotic analgesics, prepared by local pharmaceutical industries i.e. Paracetamol, Mefenamic acid and Ibuprofen have been examined for their dissolution and disintegration rates in vitro.

The different brands of each product exhibited significant difference in dissolution rate. These differences probably account for some of the conflicting clinical reports concerning the bioavailability of various tablets of Paracetamol, Mefenamic acid and Ibuprofen sold under different names.

These tablets were tested for all their physical parameters in addition to assay, disintegration and dissolution rates.

Thus a comparative study on disintegration and dissolution rates of five brands of three different non-narcotic analgesic was made to assess the quality of the tablets, manufactured by different pharmaceutical companies.

Introduction

Non-narcotic analgesics are widely used for pain killing and pyrexia and are commonly available with or without prescription. Most of them are O.T.C. products.

Analgesics are the class of drug products which are mostly prepared / manufactured by a number of local and national pharmaceutical industries. Usually

they are available as oral solids in the form of tablets. In absence of any rational drug therapy, drug monitoring system in the region and eventually lack of good manufacturing practices in most of the local companies, it is obvious that quality of these tablets are variable. Such variation exists from brand to brand not only qualitatively but also quantitatively. These variations are most commonly visible in tablet dissolution and disintegration rates and thus responsible for bioavailability problems.

The clinical effectiveness of these tablets and other pharmaceutical dosage forms of the drugs at least depends on two factors. The medication must not only be present in the labelled amount, but also must be available to the body.

Therefore one important aspect of drug dosage form development is of course, to obtain a dosage form that is absorbed in a desired fashion. In most cases this implies a rapidly and completely absorbed dosage form; this means that it is necessary to test the drug substance itself for in vivo release characteristics.

The drug absorption and physiological availability depends on having the drug substances in dissolved state; therefore suitable disintegration and dissolution characteristics are an important property of satisfactory tablets.

The advantages to be gained in developing *in vitrotests* that are predictive of drug absorption in man are considerable and have stimulated an overwhelming number of investigations by pharmaceutical scientists throughout the world. These efforts have focused largely on disintegration and dissolution tests. Thus dissolution rate is the most important factor from the view point of bioavailability. Any change in dissolution rate has a marked effect on bioavailability of the product.

Acetaminophen, Mefenamic acid and Ibuprofen are the most widely used non-narcotic analgesics. As a tablet dosage they are however heterogeneous system and as such they are one of the most complex class of drug products from physical point of view; since tablets are compressed systems they have a range of mechanical properties not seen in other dosage forms. Achieving satisfactory drug dissolution profile is more difficult from tablets than from any other class of oral dosage forms.

It is increasingly recognised that the physical and mechanical properties of tablets may undergo changes on aging or on exposure to environmental stresses, thus having a stability profile that affects bioavailability and other fundamental tablet properties. Thus physical and mechanical stability of the tablets are as important as

chemical stability of the tablet. It is also apparent that attempts at optimizing tablet formulation and dosage forms can only be successful as accuracy and adequacy of the physical methods used in product evaluation.

The primary objective of an *in vitro* dissolution test are to demonstrate that:

(a) Essentially 100% of the drug can be released from the dosage form,

(b) The rate of drug release is uniform from batch to batch is in the same, as the release rate from those batches, proven to be bioavailable and clinically effective.

Thus the purpose of this research is to investigate and to compare the in-vitro disintegration and dissolution rates of five different brands of Acetaminophen, Mefenamic acid and Ibuprofen. Such studies may serve as an Excellent "marker" to assess the standard of locally produced non-narcotic analgesics.

Experimental Studies

In the present studies 3 drug preparation:

1. Paracetamol tablets (Acetaminophen)
2. Ponstan tablets (Mefenamic acid)
3. Brufen tablets (Ibuprofen)

Manufactured from various pharmaceutical companies were selected and tested for the comparative studies. The studies carried out are;

1. Uniformity of weight
2. Uniformity of diameter
3. Uniformity of thickness
4. Hardness test for tablets
5. Tablet friability test
6. Disintegration test
7. Dissolution test
8. Assay studies

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Collection of Samples

Five samples of each of the 3 drugs manufactured by various companies were collected from the market of Hyderabad city.

The name of each manufacturer and the trade name of each sample with Batch No. Potency, date of manufacturing and expire date of each sample is given in the table (1).

Table 1

Showing the trade name of each product, the name of the manufacturer, batch No. Potency, Date of Manufacturing and Date of Expire.

Trade Name of Drug	Manufacturer	Batch No.	Potency	D.O.M.	D.O.E.
ACETOMAINOPHEN					
A_1 Panazam	Feroze	1359	500 mg	Dec: 89	Dec: 94
A_2 Panadol	Sterling Products Pak	DX-74-EL	500 mg	Oct: 89	Oct: 94
A_3 Paracetamol	Tabros Pharma	2268	500 mg	Oct: 88	Oct: 92-93
A_4 Paracetamol	Nicholus	19224	500 mg	Nov: 89	Nov: 92
A_5 Calpol	Wellcome	MX-2588	500 mg	Feb: 89	Feb: 94
MEFENAMIC ACID					
B_1 Ponstan	Park Davis	6493098-S	500 mg	Sep: 88	Sep: 93
B_2 Meftan	Anglo Pak	–	250 mg	Feb: 88	Feb: 93
B_3 Mefenac	Eferoze Pharm	854	250 mg	Nov: 89	Nov: 94
B_4 Novomic	Krka	130989	250 mg	Sep: 89	Sep: 92
B_5 Dolor	Adamjee	05	250 mg	Nov: 89	Nov: 91
IBUPROFEN					
C_1 Brufen	Boots	18-Y	400 mg	Nov: 89	Nov: 92
C_2 Ibuprofen	Krka	–	400 mg	Aug: 89	Aug: 92
C_3 Rumafen	Atco	9L, 065	400 mg	Dec: 89	Dec: 92
C_4 Inflam	Fisons	117	400 mg	Apr: 89	Apr: 92
C_5 Mactofen	Macter	–	400 mg	Aug: 89	Aug: 92

Apparatus and Method

1. Balance Sartorius — W. Germany
2. Vernier Caliper — 1-G-Instrumenten Gesellschaft-AG.
3. Hardness Tester — Schlevnger-ZE Switzerland.

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4.	Friability Tester	Acc: Roche Friabilator Type: 3R (J-Engeesmann Ltd.); Ludwigshafen A. Rh Germany.
5.	*Disintegration Apparatus:*	Erweka Disintegrator ZT-3.
6.	*Dissolution Apparatus*	Sandoz AG., Dissolution Apparatus Model 182-683, Switzerland.
7.	*Spectrophotometer*	DU-7 Spectrophotomer Beckman U.S.A.
8.	*Stirrer Magnetic*	Cole-Parmer, U.S.A.
9.	Disintegration test (B.P)	
10.	Dissolution test (U.S.P)	

Paracetamol

When the disintegration time of 5 brands of paracetamol was compared, it was found that disintegration time for all the 5 product of compressed tablets within the specified limits was i.e., 1-30 minutes.

However, the highest time for disintegration was taken by the sample No: A_4 (Paracetamol: Tabro), is 13 minutes (Table 2).

A comparison of the resulting data of dissolution test of different brands i.e. sample No. A_1, A_2, A_3, A_4 and A_5 was also made; and it was found that each product releases a different percentage of active ingredient in 30 minutes (Table 2). Out of which the results of 4 brands were found within the specified limits given by (B.P) i.e., 80%. Where as the amount released by sample (Paracetamol: Tabros) was found less than the specified limits i.e., 39.05%.

Assay results of 5 brands of paracetamol i.e., (A_1, A_2, A_3, A_4 and A_5) were also compared, and in this test a variation between different products was also found, but non of the sample was found out of specified limits i.e., 95-105%. However the best results were obtained with sample No.2 (Panadol: Sterling Pharma) i.e., 102% and sample No.5 (Calpol Wellcome) i.e., 104% (table 2).

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Table 2

Acetaminophen	A_1	A_2	A_3	A_4	A_5
Trade Names	Panazam	Panadol	Paracetamol	Paracetamolca	Calpol
Manufactures	Efroze	Sterling Prod: Pak	Tabros	Nicholus	Welcome
Tests Applied					
Weight Applied					
Weight Variation Test					
Average Weight	611 mg	595 mg	58 / mg	573 mg	623 mg
Weight Variation	641.5–	624.75–	610.1	601.65	654.15
Allowed	580.45 mg	562.3 mg	551.95 mg	544.39 mg	591.85 mg
Uniformity of Diameter					
Average Diameter	12.22 mm	12.15 mm	12.2 mm	12.74 mm	12.62 mm
Variation	11.61–	11.48–	11.89–	12.10–	12.24–
Allowed	12.83 mm	12.67 mm	12.81 mm	13.38 mm	12.99 mm
Uniformity of Thickness					
Average Thickness	5.48 mm	4.69 mm	4.78 mm	4.2 mm	5.16 mm
Variation Allowed	5.21–	4.46–	4.51–	3.99–	4.902–
	5.75 mm	4.93 mm	5.02 mm	4.41 mm	5.418 mm
Hardness Test	8.66 kg	7.71 kg	4.58 kg	7.63 kg	12.41 kg
Frigibility Test	0.373%	0.695%	9.38%	1.25%	2.02%
Disintegration Test	45 sec	1.30 min	4.45 min	13.0 min	2.15 min
Dissolution of Active Intgredient in 30 min	85.48%	100.18%	39.05%	100.68%	102.34%
Assay of Active Ingredient	98.10%	102.57%	96.18%	96.695%	104.93%

Mefenamic Acid

When the disintegration test results of 5 brands of mefenamic acid tablets were compared; it was found that 4 products i.e. sample No. B_1, B_2, B_4 and B_5 the disintegration time was between 1 to 3 minutes, where as one sample, No: B_2 (Meftan Anglopak) showed some what high disintegration duration i.e. 11 minutes. However all were within the specified limits, given for compressed tablets i.e. 1–30 minutes (Table No.3).

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The dissolution test results of Mefenamic acid were also compared and 4 products i.e. B_1, B_3, B_4, B_5 were found within the limits, where as the sample B_2 (Meftan Anglo Pak) had very low percentage of content, released in 30 minutes i.e. 46.37% (Table No.3)

Assay results of the 5 brands of mefenamic acid were also compared and 4 brands were found within the specified limits i.e. 95–105%. No. B_2 Product (Meftan Anglo Pak) was found lower i.e. 15.34% than the specified limits (Table No.3).

Table 3

Mefenamic Acid	B_1,	B_2,	B_3,	B_4	B_5
Test Applied	Ponstan	Mefian	Mefnac	Novamic	Dolor
Manufacturer	Park Devis	Anglo Pak	Efroze	Krka	Adamjee
Weight Variation Test					
Average Weight	578 mg	532 mg	604 mg	564 mg	573 mg
Weight Variation	606.9–	558.6–	634.2–	592.2–	601.65–
Allowed	549.1 mg	505.4 mg	573.8 mg	535.8 mg	544.35 mg
Uniformity of Diameter					
Average Diameter Variation	12.0 mm	12.16 mm	12.1 mm	12.9 mm	12.11 mm
Diameter Allowed	111.4–	11.55–	11.49–	12.51–	11.51–
12.6 mm	12.77 mm	12.71 mm	12.29 mm	12.72 mm	
Un Thickness					
Average Thickness	4.65 mm	4.41 mm	4.51 mm	4.69 mm	4.37 mm
Variation of	4.42–	4.19–	4.28–	4.46–	4.15–
Thickness Allowed	4.88 mm	4.63 mm	4.74 mm	4.93 mm	4.59 mm
Hardness Test	7.91 kg	17.27 kg	7.79 kg	9.42 kg	7.47 kg
Friability Test	0.224%	0.99%	1.38%	0.138%	0.74%
Disintegration Test	1.25 min	11.0 min	2.0 min	2.0 min	3.0 min
Dissolution Active Ingredients in 30 min	81.44%	46.38%	99.32%	82.35%	79.37%
Assay of Active in Gradient	94.63%	51.34%	99.67%	97.53%	96.21%

Ibuprofen

The disintegration test results of 5 brands of Ibuprofen were compared (table No 4). A variation in amount of active ingredient released in 30 minutes was found between each of 5 brands i.e. C_1, C_2, C_3, C_4 and C_5.

The results of all brands were found within specified limits. However, the highest time taken for disintegration was of product No. C_5 (Mactofen) i.e. 32 minutes.

The dissolution test results of 5 brands of Ibuprofen i.e. C_1, C_2, C_3, C_4 and C_5. were compared and a slight variation in the amount of active ingredient release was found to be 30 minutes.

All the 5 brands were within specified 50% limits.

However the greatest amount released was, from sample No. C_4 (Inflam: Fisons) i.e. 101.67% (Table No.4).

Assay result of Ibuprofen tablets were also compared, and a variation in potency was detected. An interesting point in assay comparison observed, was that, each of 5 brands of ibuprofen having active percentage of compound was more than the specified limit i.e. 95 to 105%.

Table 4

Ibuprofen	C_1 Brufen	C_2 Ibuprofen	C_3 Rumafen	C_4 Inflam	C_5 Mactofen
Disintegration Time	8.0 min	14.0 min	16.0%	6.0 min	32 min
Dissolution of Active Ingredient in 30 min	96.48%	84.57% min	95.16%	101.67%	94.69%
Potency or Assay of Active Ingredients	120.36	101.48	105.15%	113.91%	

Discussion and Results

Paracetamol (Acetaminophen), Ponstan (Mephenemice acid) and Brufen (Ibuprofen) are very popular non-narcotic analgesics. The prime reason for this popularity include; an ease of accurate (get versatile) dosage, good physical and chemical stability, competitive unit production cost, and an elegant distinctive appearance resulting in a high level of patient's acceptability. Among the potential disadvantages are irritant effects on the gastrointestinal nucosa by some solids and the possibility of bioavailability problems caused by the fact that both disintegration (in most cases) and dissolution must take place before the drug is available for

absorption. They are prepared as limit dosage forms of medicaments by compaction and consist of a mixture of powders which has been compacted in a die to produce a single rigid body. They are intended to be swallowed whole and to disintegrate and release their medicaments in the G.I.T. both qualitatively and quantitatively. As such the dosage forms need to be designed so that the drug is liberated from the dosage form in such a way that dissolution of drug is mazimized. In many cases of tablet production the significant factor is the need to manufacture a compact of sufficient mechanical strength having uniform weight, to withstand the rigors of processing and packing, yet capable of reproducable breakdown on administration, so as to release the drug. We must remember that the selected precompression treatment markedly affects the formulation of tablets, particularly, whether a mixture of powdered ingredient is to be used directly or whether an intervening moist granulation step is to be introduced. This the first decision to be made and will be influenced by factors besides the stability of the medicament to heat and moisture, the flow properties of the ingredient and any tendency to segregate. The various processes of tablet making including the aggregation of drug into granular particles, the use of binders, the compaction of system into a dense compact are all factors which mitigate against a rapid drug dissolution and absorption in G.I.T. In formulating and designing of tablet products as well in considering the methods of manufacture, the fact should be kept in mind that the tablet is one of the least bioavailable form of dosage form.

Evaluation of Acetaminophen, Mephenemic acid and Ibroprofen tablets has suggested that there is a variation in disintegration and dissolution times not only within different brands of some tablet but also within lot to lot. Some of the values have also been shown beyond the specified limits. For example in case of Acetaminophen i.e. Paracetamol (Sample No. A_3 ; Tabros) the amount of dissolution was less than specified limits i.e. 30 minutes.

On the other hand in case of Mefenamic acid Tablet Meftan (Anglopak S.No. B_2) have shown dissolution rate less than the specified limits. Assay results of Meftan tablets (S. No. B_3) also indicated a low percentage of active contents than the specified limits where as in case of Ibuprofen all the five brands showed a higher percentage content than the specified limits. All these values stand for the fact that overdosage might have been added in order to compensate the release of drug in G.I.T. Thus in evaluation of tablet manufacturing, there is a need to consider some new parameters, like mechanical strength or crushing strength, resistance to abration, pore size distribution, liquid penetration, structure and porosity other than conventional parameters. Most of these tests are done in pharmaceutical industry as unofficial tests. In tabulating process study of pore size distribution is now providing

useful information. Seekitk and Canderton (38) have reported that by application of porosimeter, wet and dry techniques of precompression treatment can be evaluated. These authors found that for lactose, granulation resulted in a wide pore distribution as compared to ungranulated powder. According to Nyqvist [illegible] interparticulate porosity is virtually unaffected by tabulating but interparticulate gradually get reduced in size, get Finholt (40), Gibaldi (41), Levy (42) [illegible] manufacturing processes can determine the dissolution rate of a drug from a dosage form. Whether changes in these manufacturing variables are beneficial detrimental to the ultimate bioavailability of a drug depends on the physicochemical properties of the drug and it's dosage form. Pharmacists should be aware of the fact that inert ingredients and manufacturing methods, which are usually carefully guarded trade secrets, may have possible effects on the bioavailability of the drug product they select to dispense to their patients.

References

1. Wanger, J.G. 1971 Biopharmaceutics and Relevent Pharmacokinetics. Drug Intelligence Publications Hamilton, Illins, PP. 64-97.
2. Bolhuis, G.K., Vankaimp, H.V. Lerk, C.F., and Sessink, G.M. (1982) Acta Pharm. Technol. P. 111.
3. Carmella, C., Colombo, P., Conte, U., Ferrari, F., Gazzaniga, A. LaManna, A., and Peppas, (1988) Int. J. Pharm., 44: 17.
4. Madan, P.L., (1978) Can. J. Pharm. Sci., 13: 12.
5. Wagner, J.G., (1971). Biopharmaceutics and Relevant Pharmacokinetics P. 89. Hamilton Drug Intelligence Pubs.
6. Sperandio, G.J., (1948). Eranson, R.V., and Dekay, H.G., J. Pharm. Sci., PP. 37. 71.
7. Parott, E.L., Wurster, D.E. and Higuchi, T.,
8. Nelson, E., Ibid., 46: (1957) 607.
9. Levy, G., (1961) J. Pharm. Sci., 50: 388.
10. Wagnet, J.G. (1961). ibid., 50: 359.
11. Noyes, A.A., and Whitney, W.R., (1987). The rate of sol of solid subs: in their own sol. J. Chem. Soc. 19: 930.
12. Levy, G., Leonards, J.R., and Procknal, J.A., (1965). J. Pharm. Sci., 54: 1719.
13. Wagner, J.G., (1971). Generic Equivalence and inequvivalence of oral products, in biopharmaceutics and Relevant Pharmacokinetics, Drug Intelligence Publication, Hamilton, Illinois. PP. 135
14. Barr, W.H., (1972). Pharmacology, 8: 55.
15. Nelson, E.J., (1958). Am. Pharm. Assoc., Sci. Ed., 47: 297.
16. Levy, G., J. (1961). Pharm. Sci., 50: 388.
17. MacDonland, H., Pisano, F., Burger, J., Dornbuch, A., and Pelcak, E., (1969). Drug Inf. Bull.
18. Bergan, T., Oydvin, B., and Lunde, I., (1960). Acta Pharmacol. Toxicol., 33: 138.

19. **Sulvian, T.J. Sakmar, E., Wagner, J.G.: (1976).** Comparative Bioavailability: A new type of In Vitro–In Vivo correlation Exemplified by prednisone. *J. Pharmacokinet. Biopharm.*, **4**: 173.

20. **Milsap, r.L., et. al., (1979)** Comparison of two dissolution apparatuses with correlation of In–vitro–In Vivo data for prednisone and prednisotone, tablets. *Biphatm. Drug Dispos.*, **1**: 3.

21. **Cabana, B.E., and Prasad, V.K. (1976).** Presentation at the Alpha. Academy of Pharm. Sci., 21st Nat. Meeting, Orlando, Fla., Nov., **16**:.

22. **Bates, T.R., Lambert, D.A., and Johns, W.H., (1969).** J. Pharm. Sci., **58**: 1468.

23. **Gibaldi–M and Weintraub, (1970).** H., J. Pharm. Sci., **59**: 725.

24. **Wruble, M.S., (1930).** Am. J. Pharm. **102**: 318.

25. **Maney, P.V., and Kuever, R.A., (1941).** J. Pharm. Sci. **30**: 276.

26. **Melnick, D., Hochberg, M. and Oser, B.L., (1945).** J.A., J. Nutr., **30**: 67 (1945)., CA, 4929.

27. **Chapman, D.G., Crisatio, R., and Campbell, (1954).** J.A., J. Pharm. Sci. **43**: 297.

28. **Morrison, A.B., Chapman, D.G., and Campbell, (1959).** J.A., J. Pharm. Sci., **48**: 634.

29. **Swintosky, J.V. et al., (1954).** *ibid., 66: 399.*

30. **Juncher, H. and Ressehov. F., (1957).** Antibiot. Med., **4**: 494.

31. **Chulski, T. et al., (1963).** *Nature, 198* 450.

32. **Levy, G., and Gumtow, R.H. (1963).** Effects of certain tablet Formulation Factors on Dissolution rate of active ingredients III. Tablet Lubricants J. Pharm. Sci. **52**: 1139.

33. **Levy, G: Amer (1963).** J. Pharm. 135, 78.

34. **Shah, S.A. and Parrott, E.L., (1976)** J. Pharm. Pharmacol., **19**: 729.

35. **Mitchell, A.G. and Saville, (1976)** D.J., J. Pharm. Pharmacol., **19**: 729.

36. **Leeson, L.J. and Cartstensen, J.T. (1976).** Eds., Dissolution technology, Industrial Pharmaceutical Technology Section, Pharmaceutical Sci. Washington, D.C., P. 119.

37. **Solvang, S. and Finholt, (1970)** P: ibid, **59**: 49.

38. **Selkirlc A.B. and D. ganderton, (1970)** J. Pharm. Pharmacol., **22**: 798.

39. **Nyquist, H. (1986)** Drug Dev Ind. Pharm., **12**: 953.

40. **Finholt, P. L.J. Lecson and J.T. Corstensen, (1974)** eds., Academy of Pharmaceutical Sciences, American Pharmaceutical Association, Washington D.C., PP. 1–35.

41. **Gibaldi, M. (1976)** Bio–Pharmaceutics, in the theory and Practice of Industrial Pharmacy, (L. Lechman, H.A. Liberman and J.L., Kanig, eds,) Lea and Febiger Philadelphic, PP. 78–140).

42. **Levy, G. (1970)** 2nd Ed., (J.B. Spronils Ed), J.B. Lippincott, Philadelphia, PP. 36–102).

43. **Davis, S.S. (1985)** Journal of Controlled release, **2**: 27–38.

44. **Milogibaldi (1984)** *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd Edition, LEA & Febiger Publishing Company Philadelphia.

45. **Alfonso. R. Gennaryo, (1985),** *Remigton's Pharmaceutical Sciences'* 17th Ed. Mack Publishing Company, Easton, Pensylvania.

46. **Rawlins E.A. (1988)** *Beultey's Textbook of Pharmaceutics*, 8th Edition, EL. BS/Baillliere tindall.

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