International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 01-09-2024, Accepted: 02-10-2024, Published: 17-10-2024
Volume 9, Issue 4, 2024, Page No. 9-13

Formulation development and characterization of PPIs Pantoprazole as orodispersible tablets using combination of methods and super disintegrants

Ajay Kumar Yadav[1*], Abdul Hafeez[1], Vikash Gupta[2]
[1] Department of Pharmaceutics, Glocal University Pharmacy College, Saharanpur, Bhopal, Madhya Pradesh, India
[2] Department of Pharmacy, KNP College of Pharmacy, Misrod, Bhopal, Madhya Pradesh, India

Abstract
Aim: It is a research work of preparing ODTs of pantoprazole as a model PPI using direct compression technique and sublimation employing various super disintegrants.
Method: ODT formulations were developed according to the direct compression and sublimation method, and the pre-compression parameters such as bulk density, tapped density, the angle of repose, Carr's Index, and Hausner's ratio were evaluated. Characterizations of the formulated ODTs involved colour, shape, hardness and friability, tablet thickness and weight variation, drug content homogeneity, in-vitro dispersion time and in-vitro dissolution rate. FTIR was used to investigate drug-excipient interaction and stability test were done on the selected formulations through short term accelerated stability studies.
Result: In the ODTs prepared the disintegration time and the release time were also very less as desired for better patient compliance.
Conclusion: It was possible to evaluate that study samples of direct compression and sublimation with different super disintegrants are efficient in the formulation of ODTs contained pantoprazole used as PPI due to the fast disintegration and the property of immediate release.

Keywords: Pantoprazole sodium, ODTS, proton pump inhibitors, immediate release, super disintegrant

Introduction

Stated in other words, Orodispersible Tablets (ODTs) [1] can be described as the new breakthrough in dosage forms, the purpose of which is to bring comfort to patients [2]. These tablets are designed to either dissolve or disintegrate in the saliva in the mouth without the use of water and are especially useful for patients who experience a problem in swallowing standard tablets as described by the paediatric, geriatric or psychiatric patients. Different process and formulations excipients used in the preparation of ODTs with an aim of fast disintegration. Such techniques as direct compression, sublimation, lyophilization, and spray-drying is used in the process while super disintegrants sweeteners, flavours and lubricants may be added to the formulation to help in hastening the disintegration of the tablet [3, 4]. The main benefits of ODTs are its portability, quicker effect, increase inpatient compliance and variable dosing frequencies [5]. The aim of the present study is to develop ODTs containing various types of super disintegrants and C-PPIs via the direct compression and sublimation technique, and to assess disintegration ability with immediate release characteristics.

Materials and method

In this research work, an example of the class of PPIs which is Pantoprazole Sodium was used as the drug under consideration. All chemicals/Powder used for this study was collected from Vasudha Pharma Chem Ltd., Vizag, and the drug Pantoprazole Sodium was of analytical grade. The polymers were purchased from K. P. Pharmaceuticals New Delhi, India and Vara Pharma chem Mumbai India. Ltd all other excipients and reagents used were of analytical reagent grade and were purchased from authorized source.

Pre formulation studies

Characterization of pantoprazole sodium and compatibility study

This was ascertained by determining it melting point. Further, FTIR absorption spectrum of Pantoprazole was scanned with KBr disc between wave No. 4000 and 400 cm-1. This was also employed to determine the interaction between drug with polymers and other excipients employed during formulation [6].
Other parameters analysed in order to assess the formulated blend included Angle of Repose (θ), Bulk Density, Carr's Index and Hausners Ratio.

Post formulation studies

Development of Oro dispersible tablets from the combination of various super disintegrants using method. Here in this approach Pantoprazole Sodium ODTs were prepared by direct compression and sublimation method using two different super disintegrants in the ratio 1:1. Each of the ingredients was individually sieved through 60# mesh sieve and retrieved in a bowl. The drug was weighed together with the other excipients and added into the container in geometrical manner. This had to be done in order to mix all the ingredients in the cocktail properly and the mixture was shaken for few minutes. These tablets were compressed and their differential properties are stated in the Table 1 using a flat face 16. The tablets were prepared with ten station Rimek tablet compression machine (Karnavati Engineering Ltd. Ahmedabad, India) with 4 × 8 mm flat oval punch to get tablets of 1300 mg weight [7].
The different approaches used are mentioned as:
Approach 1: Super disintigrant with direct compression method.

Approach 2: Combination of different superdisintegrants

Approach 3: Sublimation method.

Approach 4: Combination of superdisintegrants and sublimation method.

Approach 5: Treated Natural gums used as superdisintegrants.

Total 27 formulations were prepared F1 to F27 listed in table 1 and 2 under.

Table 1: Formulation combination for F1 to F16; F21 to F23; F26 and F27

Ingredients	Pantoprazole (in mg)	Mannitol DC (mg)	Excipients in mg	
F1	18	76.5	-	
F2	18	63.5	12	Crospovidone (CP)
F3	18	37.5	38	
F4	18	11.5	64	
F5	18	63.5	12	Sodium Starch Glycolate (SSG)
F6	18	37.5	38	
F7	18	11.5	64	
F8	18	63.5	12	Croscarmelose Sodium (CCS)
F9	18	37.5	38	
F10	18	11.5	64	
F11	18	63.5	12	Hydroxypropyl Cellulose (L-HPC)
F12	18	37.5	38	
F13	18	13.5	64	
F14	18	63.5	12	Pregelatinized Starch
F15	18	37.5	38	
F16	18	11.5	64	
F21	18	11.5	64	Camphor
F22	18	11.5	64	Thymol
F23	18	11.5	64	Menthol
F26	18	11.5	31.5	Treated Gaur
F27	18	11.5	31.5	Treated Agar

Formulations containing combination of two superdisintegrants are:

Table 2: Formulation combination for F17 to F20; F24 and F25

Formulation	Pantoprazole	Mannitol DC	1st Excipient		
			SSG	2nd Excipient	
F17	18	11.5	31.5	31.5	CCS
			CP		
F18	18	11.5	31.5	31.5	SSG
F19	18	11.5	31.5	31.5	CCS
F20	18	11.5	31.5	31.5	L-HPC
F24	18	11.5	31.5	31.5	Camphor
F25	18	11.5	31.5	31.5	Menthol

While the amount of other ingredients used in all the 27 formulations are as under:

Table 3: Amount of additional excipients used in all formulations from F1 to F27

Ingredients	Amount in mg
Aspartame	52
Talc	26
SSF	13
Sodium Bicarbonate	585
Potassium Bicarbonate	520
Flavour	6.5

Evaluation of tablets

Uniformity of thickness

Using a vernier caliper, the crown thickness of an individual tablet can be determined while enabling the determination of the variety between the tablets. Other methods used in production control include; placing 5 or 10 tablets in a holding tray whereby the total crown thickness of the tablets can be measured using the sliding caliper scale. Since it is an incremental measurement the thickness of the tablet was measured using vernier caliper [8].

Hardness test

Tablets need certain degree of strength, or hardness withstanding friability to bear mechanical stress inherent to strength, or hardness with standing the mechanical stress during handling in manufacturing, packaging and transport. The tablets hardness was measured by using Monsanto Hardness tester. It is indicated in Kg/cm2. Each formulation was prepared and three tablets were selected randomly from each of the formulations and the mean with standard deviation was determined [9].

Friability test

The process through which all or part of the surface of tablets get discolored and or get laminated or broken as an effect of shock or attrition. Friability of tablets was then assessed using Roche friabilator. It is in percentage (%) It gives the percentage proportion of the total population which comprises the residual risks in the organization. A systematic account of the experiment Three sets of ten tablets were each weighed [W (initial)] and then transferred into friabilator. The speed of the friabilator was maintained at 25 rounds per minute for four minutes or until the sample made 100 revolutions. The amount of loss by effluxion of time it was possible to weigh the tablets again another time, thus obtaining the value of W (final) [10]. The percentage friability was then calculated by,

$F = [(Wi – Wf)/Wi] \times 100$

Weight variation test

Random samples from each formulation of the tablets were selected, and reweighed to determine weight variation. The U. S Pharmacopoeia provides a little margin in the weight of a tablet in terms of standards. In all the formulations, the tablet weight was greater than 324 mg and therefore 5% maximum variation was permitted [11].

Drug Content Uniformity

The content uniformity test was applied in the process to confirm that each of the tablets had the corresponding quantity of drug substance with little differences between the tablets in a batch. For the content uniformity test, 30 tablets were taken for C/U test while 10 individual tablets were taken for the same. At least 9 had to assay within ± 15 % of the declared potency and none of them placed below ±25%. Twenty tablets were found to be weighed and underwent powdering thoroughly. The reference dose of 20 mg of pantoprazole sodium was considered, and the weighed blend equivalent to that dose was dissolved in an adequate amount of 0. 1N HCl. The solution was then passed through Whatman filter paper (No.41) to the most suitable dilution with 0. In the case of 1N HCl the absorbance value was found at 281. As absorbance, the data are expressed in absorbance unit at 5 nm, by using a UV-visible double-beam spectrophotometer (UV- 1800 Shimadzu) [12].

In vitro disintegration time

The time required for disintegration of the water dispersible tablets was carried out based on the official European Pharmacopoeia Dispersible tablets monograph which prescribes the maximum disintegration time of water dispersible tablets to be not more than 3 minutes for the product (European Pharmacopoeia 2001). The disintegration apparatus (Pharma Test, Hain burg, Germany) had to be modified, since the standard glass tube is 21. 5mm in internal diameter and the tested tablets have however a mean diameter of 25mm.The disintegration was done in a beaker containing the 200ml medium. The medium was in the form of water with temperature varying between 15 to 25ºC [13]. Tablets fasted in a Japan Scientific laboratory were used; only one tablet was tested at a time and the disintegration was declared complete when small fragments were obtained.

In vitro dissolution studies

A dissolution test apparatus of USP XXIII method with dissolution media modified as mentioned earlier was used for *in vitro* release studies. For dissolution studies, normal USP XXIII dissolution apparatus was selected in which a beaker was placed. The beaker was an elongated one normally used for Thin Layer Chromatography and for other uses. Another change made was that while stirring the mixture, instead of using paddles, a basket was used because of the narrow opening of this beaker. Depending on this another beaker filled with water was poured to a level that the dissolution fluid in the beaker attained a temperature that was affirmed and maintained at 40. 1°C and the use of the rotation of the basket was maintained at 75 RPM [14]. Dissolution fluid was prepared only with 190 ml.

Stability studies

In the present study, the ODTs were packed in suitable packaging material and stored in the following environment for a period of 90 days 40 ± 10 C and Relative Humidity 75 ± 5%. These were done after 15, 45 and 90 days of preparation of the tablets, after which the tablets were retrieved and subjected to physical evaluation (Visual defects, Hardness, Friability, Disintegration, Dissolution etc.) and drug content [15].

Similarity factor

It is used mostly when you have to ensure that your formulation is similar to that which is in the market formulation [16]. The equation of similarity factor as stipulated by Moore and Flanner, is represented in Eqn

$f_2 = 50 \times \log \{[1 / (1 + (\Sigma (R_t - T_t)^2) / N)]^{1/2} \times 100\}$

Where, N = Number of experimental data.

Results and discussion

FTIR studies

FTIR is considered as the most frequently applied method used in checking compatibility as well as in identification of the drug in question [17, 18]. Pantoprazole sodium, the excipients used and the selected formulations were characterised using an infrared spectrophotometer (Shimadzu FTIR 8-400 S model). Based on the diffmpak spectra obtained for the selected formulation F3 and F4, the characteristic peak could be observed at around 8.04 ppm, same to the peak observed in the pure pantoprazole sodium and this confirmed that there was no incompatibility between the pantoprazole sodium an the excipients used. (Shown in Fig 1 to 3).

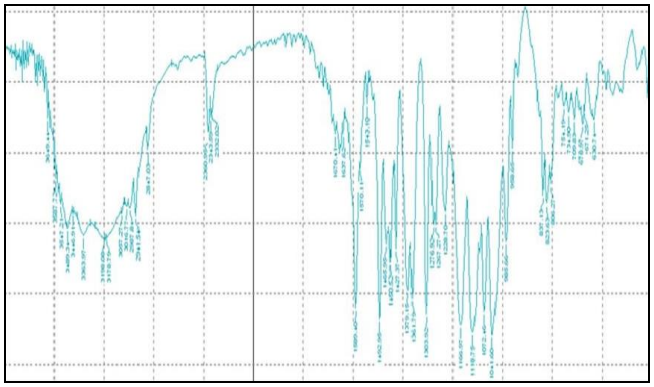

Fig 1: FTIR of pure Pantoprazole Sodium

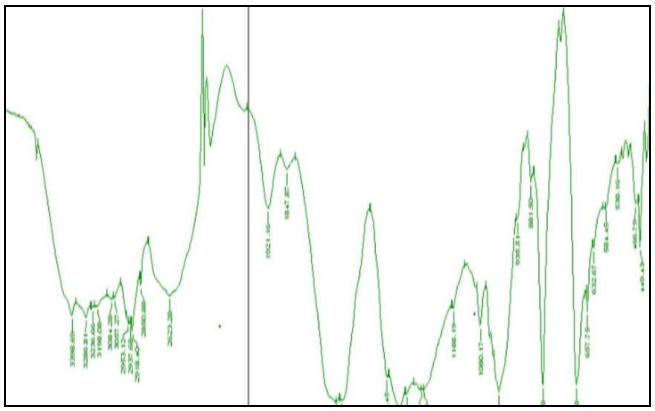

Fig 2: FTIR of Selected Formulation F3

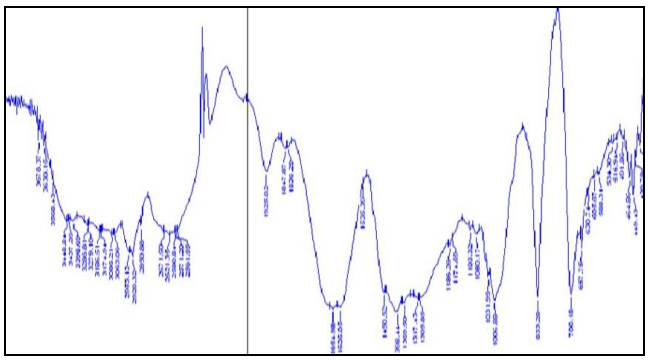

Fig 3: FTIR of Selected Formulation F4

Pre compression evaluation parameters

The pre compression parameters assessed included Angle of Repose [θ], Bulk density, Carr's index and Hausner's ratio [19 – 21]. All were found to be in agreement with the reported standards for oral quick disintegrating tablet system.

Post compression evaluation parameters

Shape of the tablets: All the tablets are flat oval in shape and the sizes are similar.

Colour of the tablets: The colour of the tablet was white and formulation prepared by addition of treated natural gums shows specific brown to black coloration depending on the colour of the dried treated gunpowder.

Thickness: It was also observed that the thickness of all the tablet was in the range of 6. 86 to 7. 05 mm.

Tablet Hardness: The tablets of each batch had the crushing strength which varied from 3. 13 to 4. 23 kg/cm2. This helps to improve the handle ability of all the batches.

Friability Test: According to the values of the described friability test they were within the range from 0. 21 to 0. 64%. All the percent friability of all the formulation were below 1% this evidenced that the tablets were mechanically sound.

Weight Variation Test: Percentages of weights for all the formulations were made as follows. All the formulated tablets complied weight variation test as the percentage weight variation was within the pharmacopoeia since the formulation blend of all the formulations had good flow hence the percentage weight deviation was within ±5% of the average weight [22]. It was also observed that the weights of all the tablets under test were homogenous with small standard deviation.

Drug content uniformity

From all the formulation percentage of the drug content was determined to be 91. 98% to 100. 94 % which comes within the IP range for enteric coated formulation of 90 to 110 % which was considered while preparing ODTs of pantoprazole sodium because ODTs of pantoprazole sodium is not official in any pharmacopoeia [23, 24].

***In vitro* disintegration Test**

This is the most important test in so far as ODT formulations are concerned [25, 26]. The studies used five superdisintegrants, three subliming agents and two treated gums for these studies. Out of all the CP, CP was selected as the best superdisintegrant as it provided the least in-vitro disintegration time. From this observation it was seen that none of the superdisintegrant provided an *in vitro* disintegration time within 180s at a concentration of 2 % except for CP. Regarding concentration, it was observed that CP was increased and *in vitro* disintegration time was reduced; least *in vitro* disintegration time was noted to be 5 % concentration.

***In vitro* dissolution studies**

All the selected formulations which cleared the *in vitro* disintegration test were subjected to *in vitro* release studies using modified dissolution assembly apparatus of USP II in 0. 1N HCl pH 1. 2 [27, 28]. Based on the *in vitro* disintegration test, *in vitro* dissolution test and the similarity factor; formulation F3 and F4 were identified as optimized formulations. Of all the formulation prepared Formulation F3 released the maximum amount of the drug. The drug release studies revealed that the maximum release for the formulation F3 was (98. 86 ± 1. 24) within 2 min and for the formulation F4 the maximum drug release (102. 52 ± 0. 23) was found within 1 min, which are also in agreement with the disintegration time obtained for respective formulations.

Similarity factor

The similarity factor of formulation F3 and F4 with respect to standard formulation "OMEZ INSTA" was 50.6033 and 72.0016. Since the similarity factors of the formulations F3 and F4 are both greater than 50, as per the USP guidelines, both these formulations are similar to the reference formulation.

Accelerated stability study

Subsequently, the selected formulations were exposed to accelerated stability studies and physical characteristics like appearance, hardness, friability, drug content, *in vitro* disintegration time and *in vitro* dissolution test was done on the formulations [29]. The formulations were kept at temperature of 40 ± 1°C and relative humidity of 75 ± 5%. All the formulations were evaluated after the time intervals of 15 days, 30 days, 45 days and 90 days. All the formulations remained unchanged in all the above parameters thus successfully passing the accelerated stability study which was carried out for a period of 90 days.

Conclusion

Respectively, it has been seen from the result of the *in vitro* disintegration test that, with the help of CP, and the mixture of super disintegrants with CP, the disintegration rates of the tablets have been found to be more effective than the other tested super disintegrants, subliming agents and treated natural gums utilized for the same purpose. Tablets prepared with CP and its mixture also revealed the faster drug release as compared to tablets prepared with other remaining super disintegrants, subliming agents and treated natural gums used as super disintegrants even from dissolution studies.

The flow properties of the formulation powder have fair flow properties which is desirable for the ODT formulations. According to the present investigation, direct compression method is the most suitable method for the preparation of ODTs. This method is also very economical as well as time saving. CP was observed to have given the best super disintegrant result among all the concentration levels with the 5% concentration had given the best result. It was also found at that time that 1.1 g of bicarbonate is the safety measure that helps to provide stability of the PPIs in the field of the acid media. The result from *in vitro* disintegration time and *in vitro* drug release reveal that the chosen super disintegrants liberate least *in vitro* disintegration time and liberate maximum amount of drug within 1 to 3 min CP level used reduces the *in vitro* disintegration time and in turn *in vitro* drug release time. Therefore, among the formulations considered the two best formulations identified were F4 and F3. Stability studies showed that the tested formulations, F3 and F4, or the formulations containing 3% and 5% CP were stable at the end of accelerated stability testing.

References

1. Edwards LD, Fletcher AJ, Fox AW. Principles and practice of pharmaceuticalmedicine. 2nd ed. London: John Wiley & Sons, 2007, 7-61.
2. Lachman L, Liberman HA, KaingJL. The theory and practice of industrial pharmacy.3rd ed. Bombay: Varghese publishing house, 1987, 293-335.
3. Liberman HA, LachmanL, Schwartz JB. Pharmaceutical dosage forms tablet. Vol. 1. 2nd ed. New York: Marcel dekker inc, 2005, 75- 77.
4. Ghosh TK, Pfister WR. Drug delivery to the oral cavity molecules to market. U.S.A: Taylor and Francis group, 2005, 261-289.
5. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth dissolving tablets I: An overview of formulation technology. Sci Pharm,2009:77:309-326.

6. Bhowmik D, Krishnakanth CB, Chandira RM. Fast dissolving tablet: An overview. J Chem Pharm Res,2009:1(1):163-177.
7. Kumaresan C. Orally disintegrating tablet-rapid disintegration, sweet taste, and target release profile. Pharm Rev,2008:6(5):7-9.
8. Bhaskaran S, Narmada GV. Orally disintegrating tablets. Indian Pharmacist,2002:1(2):9-12.
9. Swarbrick J, Boylan J. Encyclopedia of Pharmaceutical technology, 2nd ed. New York (NY): Marcel Dekker, 2002, 2623-238.
10. Mishra DN, Bindal M, Singh SK, Kumar SGV. Rapidly disintegrating tablets of Valdecoxib. Indian Drugs,2005:42:685-687.
11. Pebley WS, Jager NE, Thompson SJ. Rapidly disintegrating tablet. US Patent,1994:298:261.
12. Deepak H, Geeta A, Hari Kumar SL. Recent trends of fast dissolving drug delivery system - An overview of formulation technology. Pharmacophore,2013:4(1):1-9.
13. Bangale GS, Yadav GJ, Shinde GV, Stephen Rathinaraj B. New Generation of Orodispersible Tablets: Recent Advances and Future Prospects. Int J Pharmacy Pharm Sci Res,2011:1(2):52- 62.
14. Harsoliya MS, Pathan JK, Shruti S. A Review Formulation of Mouth Dissolving tablet. Int J Pharm Clin Sci,2011:1(1):1-8.
15. Mishra DN, Bimodal M, Singh SK, Vijaya Kumar SG. Spray dried excipient base: a novel technique for the formulation of orally disintegratinuhg tablets. Chem Pharm Bull,2006:54(1):99-102.
16. Bhowmik D, Jayakar BK. Sampath Kumar. Fast dissolving drug delivery system. Int J Pharma Res,2009:1(1):31-40.
17. Mahapatra AK, Swain RP, Revathi B, Nirisha N, Murthy PN. Orodispersible tablets: A review on formulation development technologies and strategies. Res J Pharm Technol,2013:6(9):941-953.
18. Aarti J, Joshi S, Deshmukh G. Orodispersible Tablets: A Comprehensive Review.
19. Giri T, Tripathi D, Majumdar R. Orodispersible Tablets: An Overview of Tastemasking and Evaluation Techniques. Res J Pharm Dos Form Technol,2010:2(3):225–32. Res J Pharm Tech,2014:7(3):368-375.
20. Baghel P, Roy A, Chandrakar S, Bahadur S. Fast Dissolving Drug Delivery Systems: A Brief Review. Res J Pharm Technol,2013:6(6):597602.
21. Deshpande KB, Ganesh NS. Orodispersible tablets: An overview of formulation and technology. Int J Pharm Biol Sci,2011:2(1):726-734.
22. Kumar E, Bhagyashree J. Mouth dissolving tablets – A comprehensive review. Int J Pharm Res Rev,2013:2(7):25-41.
23. Chiman B, Isha S. Development of fast disintegration tablets as oral drug delivery system - A review. Indian J Pharm Biol Res,2013:1(3):80-99.
24. Wilson CG, Washington N, Peach J, Murray GR, Kennerley J. The behavior of a fast dissolving dosage form (Expidet) followed by G-Scintigraphy. Int J Pharm,1987:40:119-123.
25. Fix JA. Advances in quick-dissolving tablets technology employing Wowtab. Paper Presented at: IIR Conference on Drug Delivery Systems. Washington DC, USA, 1998.
26. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth Dissolving Tablets I: An Overview of Formulation Technology. Scientia Pharmaceutica Sci Pharm,2009:77:309-326.
27. Jain P, Jain S, Mishra A, Pathak A. A Review on Orodispersible Tablet. Curr Res Pharm Sci,2014:4(4):99-109.
28. Kumar R, Patil MB, Patil SR, Paschpura MS. Development & characterization of melt-in- tablets of Haloperidol by sublimation technique. Int J Pharm Pharm Sci,2009:1(1):65-73.
29. Patel P, Tanwar YS, Jaimin M, Patel A. Orodispersible Tablet of Proton Pump Inhibitor Drugs: A Review. J Pharm Sci Biosci Res,2013:3(2):68-76.