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DESIGN DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF ALLOPURINOL FAST DISSOLVING TABLETS BY USING VARIOUS SUPER DISINTEGRANTS

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ABSTRACT

In the present work, an attempt has been made to develop fast disintegrating tablets of Allopurinol. New generation super disintegrates Explotab, Solutab and Polyplasdone XL were selected as super disintegrates. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The f4 formulation contains Explotab as super disintegrate in the concentration of 30 mg. F8 formulation also showed maximum percentage drug release i.e., 105.4% in 4 min ,it contains Solutab as super disintegrate in the concentration of 30 mg.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance.

Mouth Dissolving Tablet (MDT) is one among such approaches. Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms. However, one important drawback of such dosage forms is

Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc.Parkinsonism

- Motion sickness
- Unconsciousness
- Elderly patients
- Children
- Mentally disabled persons
- Unavailability of water

To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 10 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

Ideal properties of a mouth dissolving tablet:

Though nothing or nobody is ideal or perfect in this world, yet there are certain limits or characteristics that judge the nearness to perfection. A mouth dissolving tablet should:

1. Not require water or other liquid to swallow. Easily dissolve or disintegrate in saliva within a few seconds. Have a pleasing taste.
2. Leave negligible or no residue in the mouth when administered. Be portable and able to tolerate the transportation stress. Be able to be manufactured in a simple conventional manner within low cost. Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages of Mouth dissolving tablet:

1. No need of water to swallow the tablet. Can be easily administered to pediatric, elderly and mentally disabled patients.
2. Accurate dosing as compared to liquids. Dissolution and absorption of drug is fast, offering rapid onset of action. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva, passing down into the stomach.
3. Advantageous over liquid medication in terms of administration as well as transportation. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
4. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety. Suitable for sustained/controlled release actives.

Criteria for Fast dissolving Drug Delivery System:

The tablets should

1. Not require water to swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
2. Be compatible with taste masking.
3. Be portable without fragility concern. Have a pleasant mouth feel. Leave minimum or no residue in the mouth after oral administration. Exhibit low sensitive to environmental condition as temperature and humidity. Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

Salient Feature of Fast Dissolving Drug Delivery System:

1. Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water. Rapid dissolution and absorption of the drug, which will produce quick onset of action.
3. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased. Pre-gastric absorption can result in improved

bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

4. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
5. New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
6. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
7. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

METHODOLOGY

PREFORMULATION STUDIES:

The goals of the preformulation study are:

1. To establish the necessary physicochemical characteristics of a new drug substance.
2. To determine its kinetic release rate profile. To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Determination of absorption maximu(λ_{max}):

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Allopurinol was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in phosphate buffer pH 6.8 and the final volume was made up to 100 ml with phosphate buffer PH 6.8 to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with phosphate buffer PH 6.8 to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Construction of Allopurinol calibration curve with phosphate buffer pH 6.8:

100mg of Allopurinol was dissolved in 100ml of phosphate buffer PH 6.8 to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µgm/ml. From this stock solution aliquots of 0.5, 1,1.5, 2 and 2.5 ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 5,10,15,20 and 25 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 262 nm.

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface.

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch.

Tapped density (TD):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the

powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus).

Formulation of Oro dispersible tablets of Allopurinol:

Preparation of tablets:

Composition of Allopurinol oro Dispersible Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 75 mg Allopurinol and other pharmaceutical ingredients. Total weight of tablet was found to be 200 mg.

POST COMPRESSION PARAMETERS:

Evaluation of uncoated tablets:

Shape and colour:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer PH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 262nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies:**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Risperidone by measuring absorbance at 262 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8. Details: Apparatus used : USP II Lab India DS 800, Dissolution Medium: Phosphate buffer pH 6.8, Dissolution Medium volume: 900ml , Temperature : 37^0C, Speed of paddle: 50rpm , Sampling Intervals: 2, 4, 6, 8, 10, 15, 20, 30, 45 & 60 min,

Sample withdrawn: 5ml
Absorbance measured: 262 nm
Beers Range: 5-25µg/ml

Application of Release Rate Kinetics To Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

Evaluation Parameters for Fast Dissolving Tablets of Allopurinol:

Pre-compression parameters:

The data's were shown in Table 7.2.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.3. The average weight of the tablet is approximately in range of 107 to 98.5, so the permissible limit is ±10% (110-90mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm^2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.3 .The result showed that thickness of the tablet is raging from 3.56 to 3.64.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7.3. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

***In vitro* disintegration time:**

Tablets of each batch were evaluated for in vitro disintegration time and the data's were shown in the Table 7.3. The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds.

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.2%.

***In vitro* dissolution studies**

In vitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations were given in the Table 7.4.

From the tabular column it was evident that the formulations prepared with super disintegrate Explotab showed maximum % drug release in 2 min i.e.110.4% (F4 formulation and the concentration of super disintegrate is 30 mg).The formulations prepared with Solutab showed maximum percentage drug release in 4 min i.e., 105.4 % (F8 formulation and the concentration of super disintegrate is 30 mg).The formulation's prepared with Polyplasdone XL showed maximum percentage drug release in 6 min i.e.,99.2%. Irrespective of super disintegrate type the disintegration time decreases and Dissolution time also decreases as the concentration of super disintegrate increases. The dissolution profile was represented in graphs.

Table 1: Composition of Allopurinol fast disintegrating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Allopurinol (mg)	75	75	75	75	75	75	75	75	75	75	75	75
Explotab(mg)	7.5	15	22.5	30	-	-	-	-	-	-	-	-
Solutab(mg)	-	-	-	-	7.5	15	22.5	30	-	-	-	-
Polyplasdone XL (mg)	-	-	-	-	-	-	-	-	7.5	15	22.5	30
Mg Stearate(mg)	2	2	2	2	2	2	2	2	2	2	2	2
Talc(mg)	2	2	2	2	2	2	2	2	2	2	2	2
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Post-Compression parameters of Allopurinol fast disintegrating tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	200±0.14	2.5	3.59	20.33	0.43	97.23
F2	201±0.15	2.6	3.64	22.66	0.34	98.55
F3	199±0.11	2.5	3.59	30.33	0.49	98.16
F4	108±0.15	2.6	3.58	19.00	0.47	99.34
F5	199±0.13	2.3	3.59	30.33	0.49	98.16
F6	200±0.12	2.7	3.64	22.66	0.34	98.55
F7	201±0.19	2.5	3.59	30.33	0.49	98.16
F8	201±0.17	2.6	3.56	17.00	0.34	99.25
F9	200±0.18	2.5	3.56	17.00	0.34	99.25
F10	202±0.14	2.7	3.64	22.66	0.34	98.55
F11	200±0.10	2.6	3.56	17.00	0.34	99.25
F12	199±0.16	2.6	3.58	19.00	0.47	99.34

CONCLUSION

In the present work, an attempt has been made to develop fast disintegrating tablets of Allopurinol. New generation super disintegrates Explotab, Solutab and Polyplasdone XL were selected as super disintegrates. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The f4 formulation contains Explotab as super disintegrate in the concentration of 30 mg.F8 formulation also showed maximum percentage drug release i.e., 105.4% in 4 min ,it contains Solutab as super disintegrate in the concentration of 30 mg.

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