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Comparative study of post-compression parameters of branded and generic product containing metformin hydrochloride

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Abstract:

Metformin hydrochloride (HCl) belongs to biguanides and used to treat type 2 diabetes mellitus (T2DM). Various brands and generic version of metformin hydrochloride tablets are available in the market with a common claim that they are all bioequivalent. The main objective of the present experiment was to evaluate post compression parameters of brand, generic and self- prepared metformin hydrochloride tablets containing 500 mg of drug and to determine whether all the formulations used were equivalent or significantly different. Tablets were prepared by direct compression method. In the preparation of the metformin hydrochloride tablets microcystalline cellulose, potato starch and crospovidone were the main ingredients. All the formulation including branded, generic and self-prepared metformin hydrochloride were evaluated for post compression parameters like hardness, weight variation, drug content, disintegration time and *in vitro* dissolution profile and results were found to be within the prescribed limit. There was no significant difference between drug release profile of brand and generic product procured from market. Formulations A1 and A2 has taken less time to disintegrate as compared to formulations A3 and A4; this is because of the use of super distintegrant i.e., Crospovidone. All the findings and outcomes have shown that branded, generic product and in-house formulations exhibit good response.

Keywords:

Metformin hydrochloride (HCL), T2DM (Type 2 Diabetes mellitus), Crospovidone, Potato starch.

1. Introduction:

The pharmaceutical industry in India was more or less non-existent prior to 1947; there were no production units of allopathic medicine in the country. Today, in the 21st century the Indian pharma sector is well recognized and is one of the largest in the world. Globally Indian pharmaceutical industry is third largest in the world by volume and 11th by value. It comprises over 3,000 pharma companies and 10,500 manufacturing facilities. It also produces drugs at around a third of the US costs and half of the European costs. The value of generic medicine exports from India has also been on the rise, growing at an annual growth rate of 22.4%. Indian pharmaceutical industry bulk profit comes from exporting generics and API to the developed market mainly US followed by UK, Germany, and Brazil etc. The Indian generics market is growing day by day with Indian pharmaceutical companies seeking more abbreviated new drug application approvals (ANDAs) in US in major segments such as cardiovascular, antibiotics and other groups.

Generic drug is one that is similar to an innovator drug product in terms of dosage form, route of administration, quality, performance and intended use. The generic drugs which have the same chemical composition as branded drugs and sold under their chemical name. It is a medication created to be the same as an existing approved brand-name drug in the dosage form, safety, strength, route of administration, quality, performance and intended use. It works in the same way and provides the same clinical benefit as its brand name version. For examples; diclofenac sodium a generic name for branded version of Cataflam.

A generic drug is a medication created to be the same as an existing approved brand-name drug in the dosage form, safety, strength, route of administration, quality, performance and intended use. A generic works in the same way and provides the same clinical benefit as its brand name version.

In India, the approval, production, and marketing of quality generic products at reasonable price are ensured by the central drug standard control organization (CDSCO). Indian regulatory authority requires that a generic medicine must meet certain regulatory criteria. The major regulatory requirement for generic drug product approval is a generic product must

1. Contain the same active ingredients as the innovator drug
2. be identical in strength, dosage form, and route of administration
3. Be bioequivalent.
4. Be manufactured under the same strict standards of GMP required for innovator products

1.1. Why generic drugs are cheaper than branded version?

1. Competition among the generic drug producers also keep the costs down, once the generic is approved, multiple companies start to producing and selling drugs due to this the competition grows, which reduce the price.
2. The development of new drug requires many years with expensive clinical trials to confirm the safety and efficacy of the medicines. The generic manufacturers do not have to bear the research and development costs because the drug formula is known and the clinical trials with the branded drug are already completed. But they have to invest only in the production and quality control of medicines so that generic medicines are available at lower cost.
3. Branded name manufacturer spend loads of amount on marketing new medicines to doctors and the public, less amount of money is spent on marketing and advertising of generic drug product because brand drug is already approved as safe and effective.

Oral drug delivery is the more preferred route for the drug administration is also the largest and oldest segment of the total drug delivery market. Various types of drug delivery systems are available to get better therapeutic action of drug, out of which immediate release drug delivery system is gaining more importance because of their wide advantages over others like ease of administration, convenience and noninvasiveness. Immediate release tablet dosage forms are those which dissolved and get rapidly disintegrate to release the medicaments to produce rapid action. For immediate release tablet disintegrates play a major role in ensuring that tablet matrix break up on the contact with the fluid present in the stomach to allow the release of active component which then become available in whole or in part, for absorption from gastrointestinal tract.

The aim of this study is to compare post compression parameters between brand drug product, generic drug product and in-hose formulations of Metformin Hydrochloride. Metformin was discovered in 1922, study in humans began in1950s by French physician Jean Sterne. It was introduced in France in 1957 and in the United States 1995. Metformin is believed to be the most widely used medication for diabetes which is taken by orally. It is an oral hypoglycemic drug that has been used for the management of the noninsulin-dependent diabetes mellitus with usual dose of 2 gm/day and the maximum dose up to 3 gm/day.

2. Materials and Methods:

2.1. Materials:

Glyciphage is branded drug product manufactured by Franco-Indian pharmaceutical pvt. Ltd. Metformin hydrochloride is a generic version manufactured by Glenmark Generics was procured from the local market. Metformin Hydrochloride was gifted by Wynclark Pharmaceuticals Pvt Ltd. Microcrystalline Cellulose, Crospovidone, Potato starch, Magnesium stearate and Talc were obtained from SD Fine Chemicals, Mumbai.

3. Method:

3.1. Preparation of phosphate buffer (pH 6.8):

28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate were dissolved in sufficient water and volume made up to produce 1000 ml of phosphate buffer (pH 6.8).

3.2. Calibration curve of metformin hydrochloride:

The drug was accurately weighed (50 mg) using the digital balance and it was transferred to 50 ml volumetric flask. This was dissolved by adding the little amount of phosphate buffer (pH 6.8) solution. The final volume was made up to 50 ml with water to get a stock solution-A (1000 µg/ml). 10 ml of drug solution was pipetted out from this stock solution- A into 100 ml volumetric flask and it was made up to the final volume by adding phosphate buffer (pH 6.8) solution to get stock solution-B (100 µg/mL). Further series of dilutions were made from stock solution-B with phosphate buffer (pH 6.8) solution only to obtain the solutions in the range of 0-10 µg/mL of concentration. The absorbance of the samples was analyzed using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan) against blank solution at 236 nm.

3.3. Preparation of tablets:

Metformin hydrochloride and selected excipients were mixed as per the formulation table using mortar and pestle. From above mixture required quantity of powder was compressed into a tablet using single station punching machine with 12 mm flat faced punch sets.

Table. 1: Formulations table

	Formulation

Ingredients (mg/tablet)	**Brand product**	**Generic product**	**A1**	**A2**	**A3**	**A4**
Metformin Hydrochloride	500	500	500	500	500	500
Microcrystalline Cellulose	_	_	80	60	80	60
Crospovidone	_	_	20	40	_	_
Starch (Potato)	_	_	_	_	20	40
Magnesium stearate (%w/w)	_	_	01	01	01	01
Talc (%w/w)	_	_	01	01	01	01
Total	-	-	600	600	600	600

4. Evaluation of tablets:

4.1. Hardness:

The hardness of the tablet was determined by using Monsanto hardness tester. The tester consists of barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading is taken. The upper plunger was forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture was recorded. The test was performed in triplicate; average reading was taken and expressed in Kg/cm^2.

4.2. Average weight determination:

Average weight of the tablet was determined by weighing 20 tablets individually in an electronic balance and it was calculated by formula.

$$\text{Average} = \frac{\text{weight of 20 tablets}}{20}$$

4.3. Drug content determination:

The drug content was determined by crushing the tablets in glass mortar and pestle and shaking the crushed powder with 20 ml of phosphate buffer (pH 6.8) for 48 hours. The volume was made up 100 ml by using phosphate buffer (pH 6.8) and filtered using Whatmann filter paper. The extracted drug in solution was determined by analyzing the aliquot using UV- visible spectrophotometer using suitable blank at 236 nm.

4.4. Friability test:

Friability test was performed by taking 10 tablets. Pre-weight of the tablets was taken before subjecting to friability test. Weighed tablet samples were transformed into friabilator and subjected to combined effects of abrasion and shock by revolving at 25 rpm for 4 min for 100 revolutions. Samples were withdrawn after set time completions and loose dust powder was removed from the tablet and final weight is noted and substituted in the formulae.

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

4.5. Disintegration test:

The disintegration test was performed using Vasa scientific co. disintegrating apparatus. Placed one tablet in each of the six tubes of the basket and operate the apparatus using water maintained at 37±0.5ºC as the immersion fluid. Then noted down the time to complete disintegration of tablet.

4.6. Dissolution test:

In vitro dissolution was studied by using the USP apparatus II (paddle type). Tablets were placed into the 900 ml phosphate buffer (pH 6.8). The temperature was maintained at 37± 0.5 °C and stirred at a speed of 50 rpm. An aliquot of 5 ml was withdrawn at specified time intervals and replaced with fresh dissolution medium. The samples were filtered with 0.45µ Whatmann membrane filter. Amount of drug in each aliquot was assayed on a UV-Spectrophotometer at 236 nm. All the trials were conducted in triplicate and the average (±S.D) reading was noted.

5. Results:

Table. 2: Calibration curve metformin hydrochloride in phosphate buffer (pH 6.8) solution

Serial Number	**Concentration (µg/ml)**	**Absorbance (λmax 236 nm)**
0	0	0
1	1	0.097
2	2	0.172
3	3	0.229
4	4	0.303
5	5	0.368
6	6	0.433
7	7	0.504
8	8	0.588
9	8	0.632
10	10	0.707

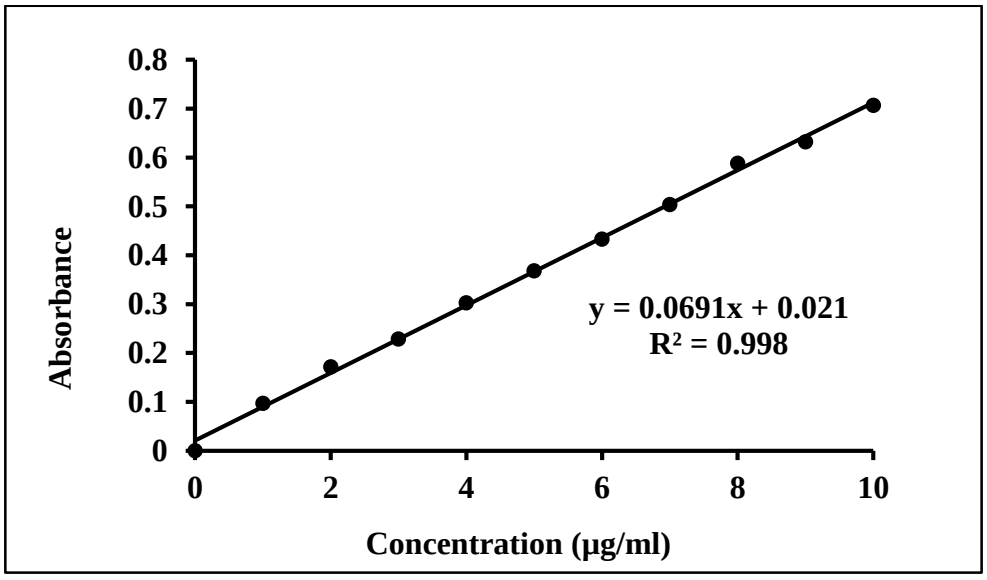

Figure. 1: Calibration curve Of Metformin Hydrochloride in phosphate buffer (pH 6.8)

Table. 3: Physical properties of tablets

Formulations	Hardness (kg/cm^2)*	Average weight of Tablets (mg)*	Drug content (%)	Friability (%)
Brand product	5 ±0.23	549.8 ±0.12	102.93	0.054
Generic product	7 ±0.36	623 ±0.23	101.06	0.833
A1	5 ±0.27	602 ±0.25	97.53	0.939
A2	4 ±0.56	597 ±1.25	95.51	0.956
A3	4 ±0.26	610 ±0.65	94.93	0.978
A4	5 ±0.51	607±0.59	97.82	0.847

6. Disintegration Test:

Table. 4: disintegration time

Formulations	Disintegration time (mins)*
Brand product	13 ±0.42
Generic product	11 ±0.49
A1	4.1 ±0.78
A2	2.1 ±0.86
A3	8.5 ±1.2
A4	5.18 ±0.8

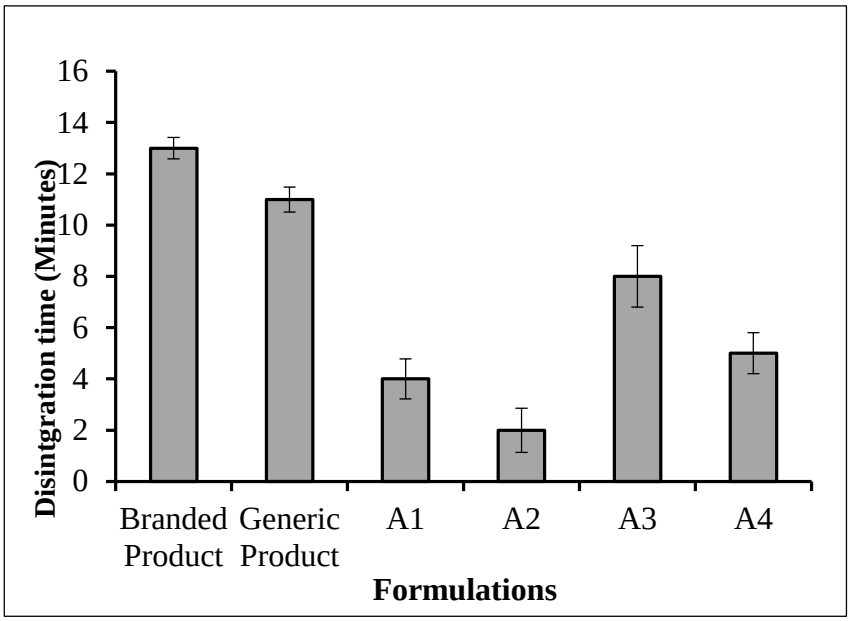

Figure. 2: Comparison plot on disintegration time

6.1. In vitro dissolution studies:

Table. 5: In vitro drug release study of Brand, Generic, A1, A2, A3 and A4 in phosphate buffer

Time (min)	Cumulative % Drug Released					
	Brand	**Generic**	**A1**	**A2**	**A3**	**A4**
0	0	0	0	0	0	0
15	69.92 ±0.12	69.71 ± 0.23	74.34 ±0.35	85.01 ±0.23	73.21 ±0.19	73.89±0.26
30	87.30 ±0.24	84.24 ±0.15	90.80 ±0.25	95.84 ±0.25	79.92 ±0.36	83.07±0.29
45	97.87 ±0.14	90.66 ±0.35	97.73 ±0.56	108.36 ±0.29	86.39 ±0.99	92.57±0.56

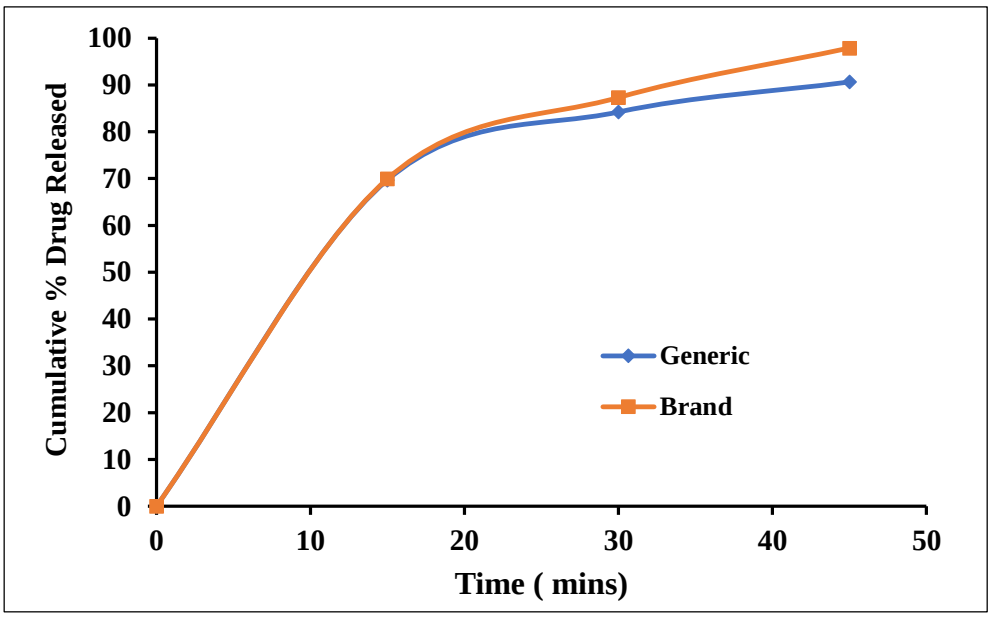

Figure. 3: Comparative graph on in vitro drug release profile of brand and generic in phosphate buffer

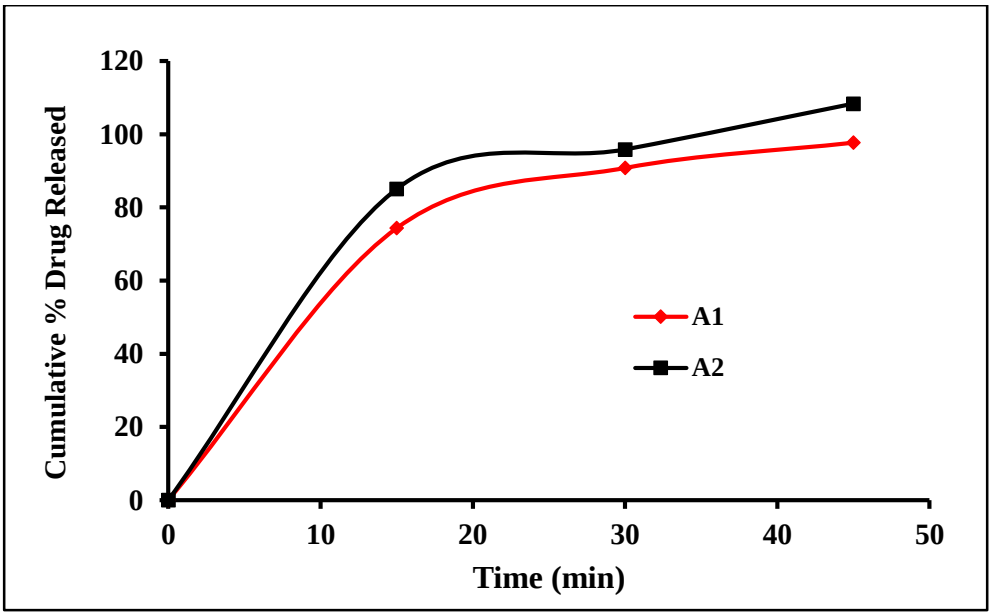

Figure. 4: Comparative graph on in vitro drug release profile of A1 and A2 in phosphate buffer

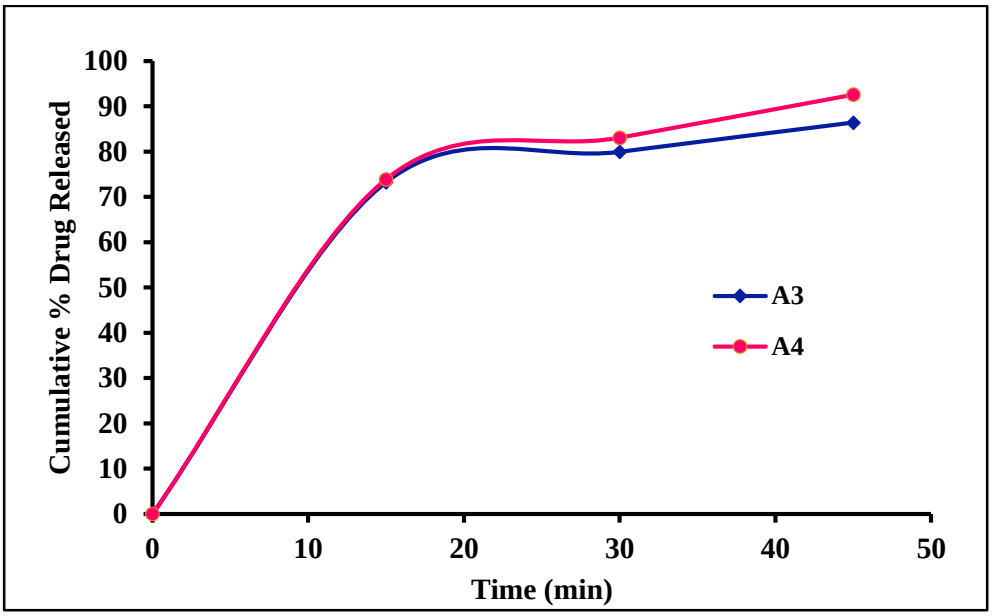

Figure. 5: In vitro drug release profile of A3 and A4 in phosphate buffer

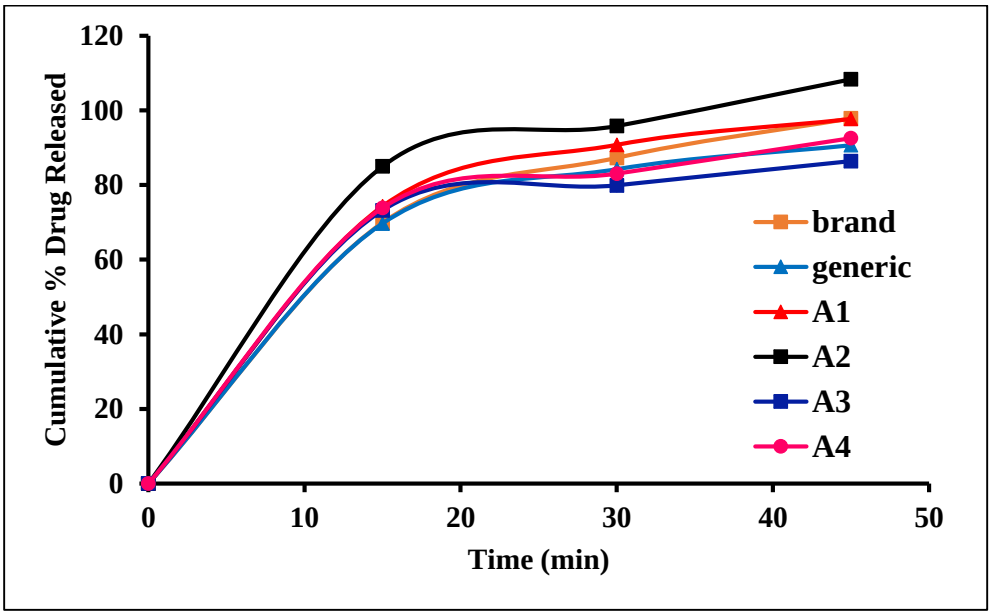

Figure. 6: Comparative graph on in vitro drug release profile of brand, generic, A1, A2, A3 and A4 in phosphate buffer

7. Discussion:

7.1. Determination of λmax of drug:

A diluted solution of Metformin Hydrochloride in phosphate buffer (pH 6.8) was scanned for absorption maxima against suitable blank between 200-400 nm using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The maximum absorbance was found at 236 nm.

7.2. Calibration curve of metformin:

The calibration curve of Metformin Hydrochloride was developed in the range of 0-10 µg/ml at wavelength 236 nm. Good linearity with a regression coefficient of 0.998 (R^2 value) was observed. The tested concentration range obeyed Beer's Lambert law (Fig. 1).

7.3. Physical properties of tablets:

The hardness of all tablet formulations was found in the range of 4 to 7 kg/cm^2 (Table. 3) indicating that the hardness of prepared formulation was within the acceptable limits. The average weight of branded, generic, A1, A2, A3 and A4 were found to be 549.8±0.12, 623±0.23, 602 ±0.25, 597 ±1.25, 610 ±0.65 and 607±0.59 gm respectively (Table. 3) indicating that the prepared formulations were within the acceptable limits. Drug content (in %) for all the formulation ranged from 94.93 to 102.93. The drug content in each tablet formulation was found to be > 85%. The tablets represent unit solid dosage forms. The preparation method used for tablet formulation is expected to show higher drug content because of negligible loss during manufacturing. The percentage friability of prepared formulation is shown in table. 3. The percentage friability of all prepared tablet formulations was found in the range of 0.847 % to 0.978 % indicating that the friability was within the acceptable limits and tablets were mechanically stable. In the disintegration study, different concentration of two different disintegrants were taken and its effects on disintegration time was determined and it has been concluded that formulation A1 and A2 takes less time to disintegrate as compared to A3 and A4 as shown in (table. 4, fig. 2). Disintegration time of all formulations was found in the range of 2 -13 minutes indicating that all were within the acceptable limits.

7.4. In vitro dissolution studies:

In vitro dissolution was studied by using the USP apparatus II (paddle type). The in vitro drug release study for all tablets was performed in 900 ml phosphate buffer (pH 6.8) at 37±0.5˚C and 50 rpm. The drug release from all the formulation after 45 minutes found to be 97.87 ±0.14, 90.66 ±0.35, 97.73 ±0.56, 108.36 ±0.29, 86.39 ±0.99 and 92.57±0.56 % respectively for branded, generic, A1, A2, A3 and A4 formulations (table. 5, fig. 6). Drug release from generic product is almost similar to branded product. Among the prepared formulations A1, A2, A3 and A4 (fig. 4 and 5), A1 and A2 have shown fast drug release compared to A3 and A4, this is because of the use of crospovidone in the A1 and A2 formulations.

8. Conclusion:

In this study we compared the innovator drug product, generic drug product and prepared formulations for physical parameters. In general, the physical parameters and in vitro drug release of all the formulations were almost similar. There is no significant difference among brand and generic product.

However, with minor modifications in formulation and preparation methodology, generic product with similar drug release as that of branded product can be prepared which will possibly show bioequivalency.

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