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Design optimization and *in vitro* and *in vivo* evaluation of fast dissolving glibenclamide tablet

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Abstract
Glyburide belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The precompression blend of Glyburide soild dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend of all the batches indicates well to fair flow ability and compressibility. The formulated tablets were evaluated for various quality control parameters. An effective, pleasant tasting formulation was found to have a good hardness of 3 kg/cm2, disintegration time of 27+1 seconds and in vitro drug release of not less than 95% within 30 minutes. The drug release was found to be comparable with the marketed dispersible tablet. Our drug meets all the criteria mentioned above. Specially formulation 5 is best among all the formulations. The brands of glibenclamide tablets complied with the official specification for hardness, friability, disintegration, and assay. Difference factor (f1) values were less than 15 and similarity factor (f2) values were greater than 50 for all products of glibenclamide. The hypoglycemic effect of different products of glibenclamide tablets was evaluated on normoglycemic mice. The in vivo studies indicated that there is no significant difference in percent reduction of blood glucose level between the brands of glibenclamide and the innovator product ($p > 0.05$). Hence, based on the in vivo results and in vitro dissolution studies, the brands might be substituted with the innovator product in clinical practice. *In vitro* and in vivo methods. Friability, disintegration, dissolution, and assay for the content of active ingredients were evaluated using the methods described in the British Pharmacopeia (2009) and United States Pharmacopeia (2007).

Keywords: Design optimization, dissolving glibenclamide

Introduction
A fast dissolving system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid [1]. Recently fast dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance [2]. Pediatric and geriatric patient have difficulty in swallowing the conventional dosage forms. Fast dissolving and fast dispersing drug delivery system may offer a solution to these problems. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy [3].

Fast disintegrating tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue [4]." Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients [5]. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action [6]. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach [7]. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form.

The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute [8]. The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking [9]. In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance [10]. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets.

***In vivo* studies**

Hypoglycemic Effect of Glibenclamide Tablets on Normoglycemic Mice. Quantification of pharmacologic effect is one possible way to assess a drug's bioavailability. This method is based on the assumption that a given intensity of response is associated with a particular drug concentration at the site of action.

Pre-formulation studies

Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmax was found to be 255nm. Hence all further investigations were carried out at the same wavelength.

Tablet disintegrants

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical - chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet. The drug will dissolve at a slower rate from a nondisintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration [11].

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet [12].

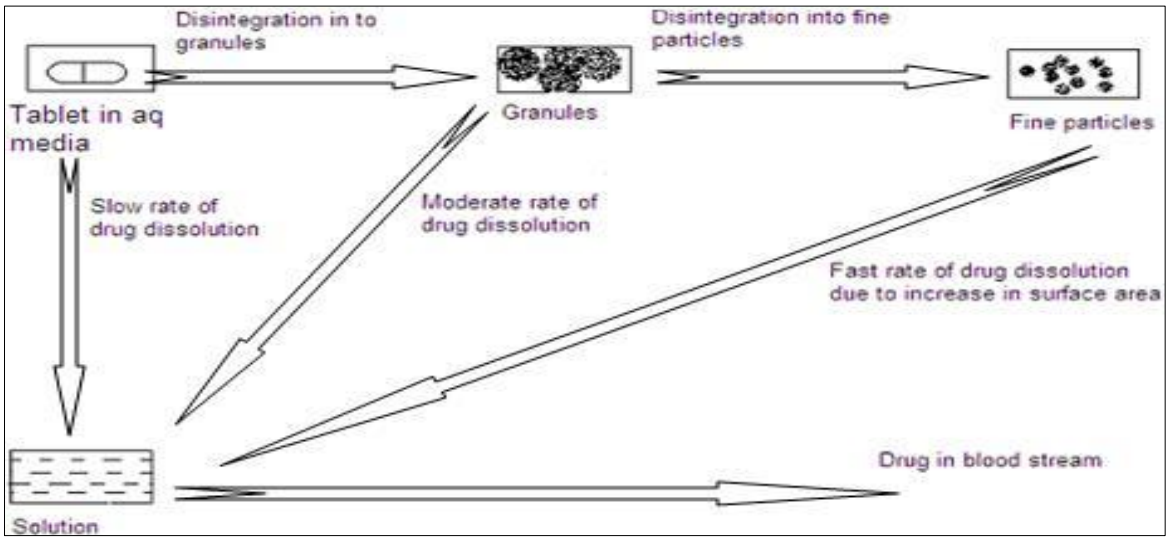


Fig 1: Schematic representation of tablet disintegration and subsequent drug dissolution

Mechanism of tablet disintegration

- Capillary action (Wicking).
- Swelling.
- Due to disintegrating particle/particle repulsive forces.
- Due to deformation.
- Due to release of gases.

By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions [13]. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity [14]. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

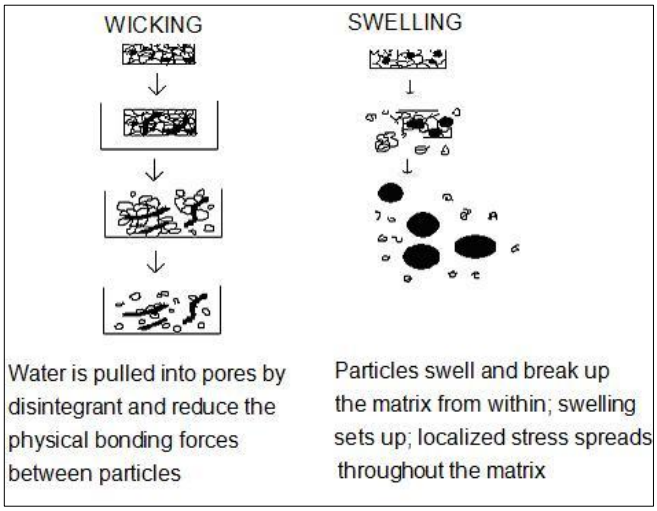


Fig 2: Disintegration of tablet by wicking and swelling

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swell able' disintegrates [15]. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. the electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water [16]. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied

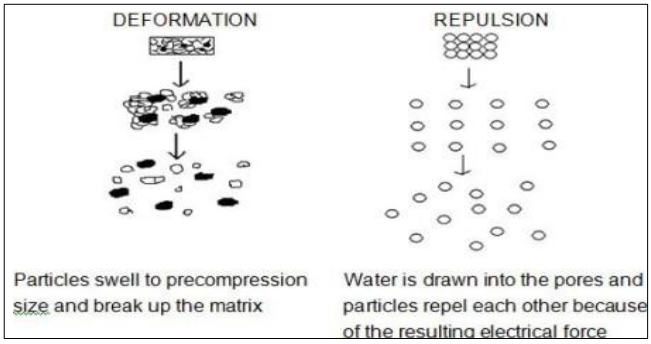


Fig 3: Disintegration by Deformation and Repulsion

Due to release of gases

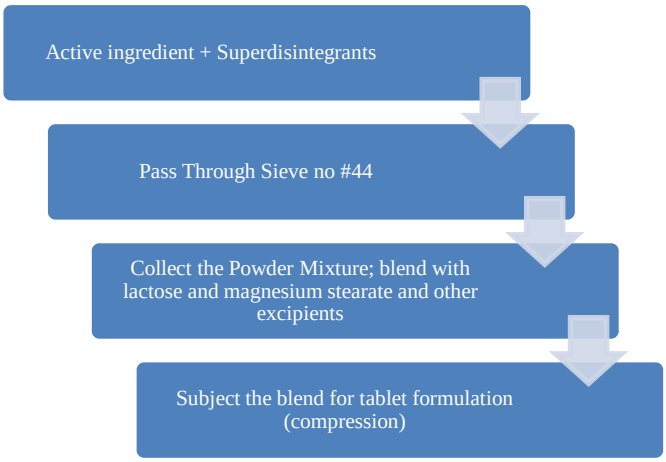
Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid [17]. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet [18]. As these disintegrates are highly sensitive to small changes in humidity level and temperature, strict control of environment is required [19] during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

Material and Methods

Glibenclamide was a gift from Amico Laboratories Ltd, starch, Lactose, Magnesium stearate, Crospovidon, Povidon-k30 and Talc were also collected Globe Pharmaceuticals Ltd, nohakhali, Bangladesh.

Direct compression

This method involves simple blending of active pharmaceutical ingredient (API) with other ingredients and direct compaction of the resultant mixture.



Preparation of glibenclamide fast dissolving tablets

All the materials were passed through 80 # screens prior to mixing. Glibenclamide, Avicel PH 102, Starch, were mixed using a glass mortar and pestle. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets using concave face round tooling on a Rimek-rotary tablet machine. In the present research work mouth dissolving tablets of glibenclamide was developed with superdisintegrant like starch in various concentration like 4%, 5%, 6%, 7% & 8% w/w by direct compression method. All formulations were evaluated for physical characteristics of compressed tablets such as weight variation, hardness, friability, content uniformity, in vitro disintegration time and in vitro dissolution study.

Table 1: Different formulation of glibenclamide fast dissolving tablet

Ingredient	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Glibenclamide	5.25	5.25	5.25	5.25	5.25
Avicel PH 102	20	20	20	20	20
Lactose	118	116	114	112	110
Crospovidon	8	10	12	14	16
Magnessium Stearate	4	4	4	4	4
Talc	2	2	2	2	2
Povidon K30	3	3	3	3	3
Starch	4	4	4	4	4
Total	164.25mg	164.25mg	164.25mg	164.25mg	164.25mg

Total observation of formulations during these process are shown in a chart which was given by the expertise of the Amico Laboratories Ltd in respect to a marketed drug product.

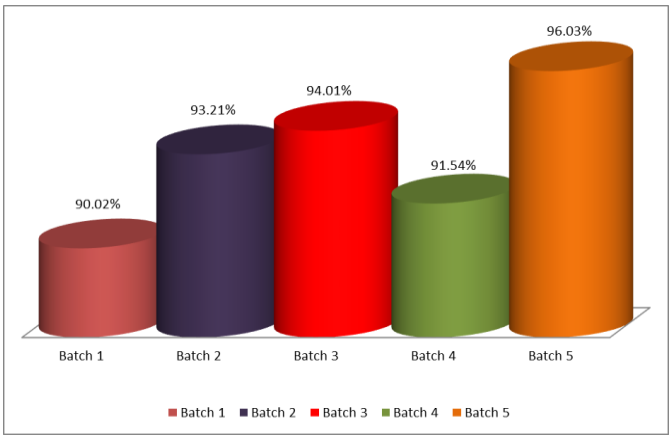


Fig 4: Comparative evaluation of all the formulations

In-vitro disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester (Electrolab, India). Distilled water at 37ºC ± 2ºC was used as a disintegration media [20] and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Table 2

Batch	In vitro disintegration time (Sec)	Result
1	1	0∞1 min
2	49	0∞1 min
3	49	0∞1min
4	49	0∞1 min
5	49	0∞1 min

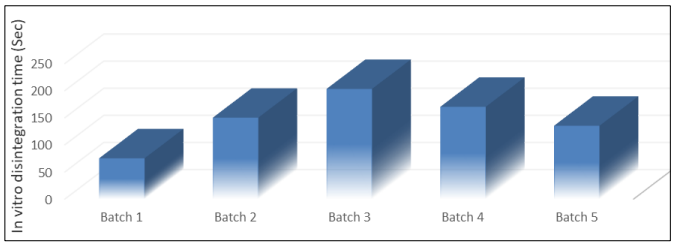


Fig 5: Comparative disintegration time of all the formulation

Content uniformity test

Assay (By UV Spectrophotometer)

The Fast dissolving tablets were prepared and evaluated for assay. Each FDT contains 10mg of Glibenclamide [21].

Preparation of standard solution

Accurately weigh and transfer about 10mg of Glibenclamide working standards into a 50ml volumetric flask. Add about 40ml 0.1M of HCl and sonicate to dissolve. Dilute to volume with Diluents and mix. Transfer 10ml of the above solution into a 50ml volumetric flask, dilute to volume with 0.1M HCl and mix.

Preparation of sample solution

Transfer 10 tablets into a mortar and crushed into fine powder blend. Weigh 560mg equivalent sample from this and transfer into a 50 ml volumetric flask. Add about 40ml 0.1M of HCl and sonicate to dissolve. Dilute to volume with Diluent and mix and then filter the solution. Transfer 10ml of the above solution into a 50ml volumetric flask, dilute to volume with 0.1M HCl and mix [22].

Procedure

Flush the UV Spectrophotometer cuvettes thoroughly with water followed by HCl. Stabilize the system for not less than 30minutes with blank solution (0.1 M HCl). Samples are typically placed in the cuvettes containing standard solution and blank as a reference in another cuvette, this is measured against the sample solution. The absorbance of both standard and sample solutions is noted at 286.00nm and drug content is estimated as

$$\text{Glibenclamide} = \frac{sample\ absorbance}{standard\ absorbance} \times \frac{standard\ weight}{sample\ weight} \times \frac{standard\ potency}{100} \times \text{average tablet weight}$$

And as

$$\text{Glibenclamide} = \frac{Result}{99.10\%}$$

Table 3

Sample ID	Wave length	Glibenclamide	Glibenclamide
1	300	1.611g (average)	161mg/tab
2	300	1.633g (average)	163mg/tab
3	300	1.644g (average)	164mg/tab
4	300	1.633g (average)	163mg/tab
5	300	1.633g (average)	163mg/tab

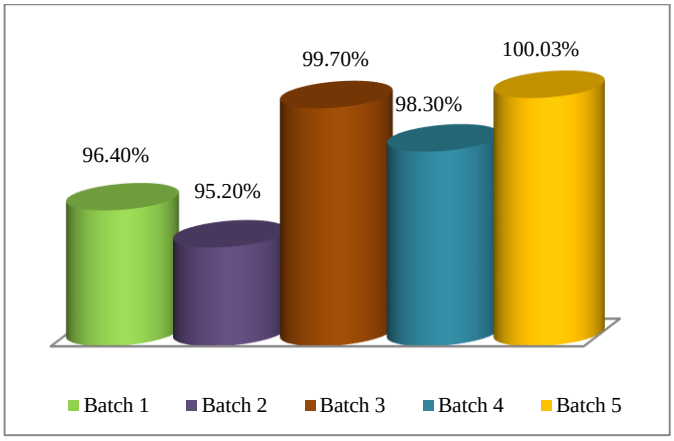


Fig 6: Our tablet acceptable limit is 95% -105%.so our all formulations are within our limit and among them formulation 5 is best.

In Vitro Dissolution Study

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

Test Conditions

a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

Procedure

1) After 45 minutes withdraw a 20 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 286 nm, Appendix II B using dissolution medium in the reference cell.
2) Measure the *absorbance* of a 0.001% w/v solution of *Glibenclamide BPCRS* in the dissolution medium using dissolution medium in the reference cell.

Determination of Content

Calculate the total content of Glibenclamide, in the medium from the absorbances obtained and using the declared content of $C_{22}H_{24}ClN_5O_2$, in *Glibenclamide BPCRS*.

Related Substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

1) To a quantity of the powdered tablets containing the equivalent of 50 mg of Glibenclamide add 10 mL of a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*, mix with the aid of ultrasound for 20 minutes and filter through a glass microfiber filter (Whatman GF/C is suitable).
2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*. Dilute 1 volume of the resulting solution to 2 volumes with the same solvent.
3) 0.01% w/v of *Glibenclamide BPCRS* and 0.015% w/v of *Glibenclamide EPCRS* in a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol.*

Chromatographic Conditions

a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).
b) Use gradient elution and the mobile phases described below.
c) Use a flow rate of 1.5 mL per minute. Equilibrate the column for at least 30 minutes with *methanol* and equilibrate with the initial mobile phase for at least 5 minutes.
d) Use an ambient column temperature.
e) Use a detection wavelength of 280 nm.
f) Inject 10 µL of each solution. Inject a mixture of equal volumes of 0.01M hydrochloric *acid* and *methanol* as a blank prior to the solutions.

Mobile Phase

Mobile phase A *Methanol.*
Mobile phase B 0.5% w/v solution of *ammonium acetate*.

Table 4

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0	30	70
10	100	0
12	100	0

System Suitability

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution *factor* between the two principal peaks is at least 2. If necessary adjust the concentration of *methanol* in the mobile phase or adjust the time programme for the linear gradient.

Limits

In the chromatogram obtained with solution (1):
The area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);
The sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).
Disregard any peak in the chromatogram obtained with the blank solution and any peak with an area less than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.05%).

Assay

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

1) Add sufficient *methanol* to 10 whole tablets to produce a solution containing 0.02% w/v of Glibenclamide, mix with the aid of ultrasound for 20 minutes and filter through a glass microfiber filter (Whatman GF/C is suitable). To 50 mL of the filtrate add 1 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 100 mL.
2) 0.0127% w/v of *Glibenclamide BPCRS* in a mixture of equal volumes of 0.002M *hydrochloric acid* and *methanol.*

Chromatographic Conditions

The chromatographic procedure described under related substances may be used.

Determination of Content

Calculate the content of $C_{22}H_{24}ClN_5O_2$ in the tablets using the declared content of $C_{22}H_{24}ClN_5O_2$ in *Glibenclamide BPCRS*.

Table 5: Evaluation of In Vitro Dissolution of Glibenclamide

Time (min)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
15	163.44mg	163.54mg	161.98mg	163.54mg	163.18mg
30	162.5mg	163.3mg	163.74mg	162.24mg	162.88mg
45	163.42mg	164.1mg	163.18mg	163.84mg	162.46mg

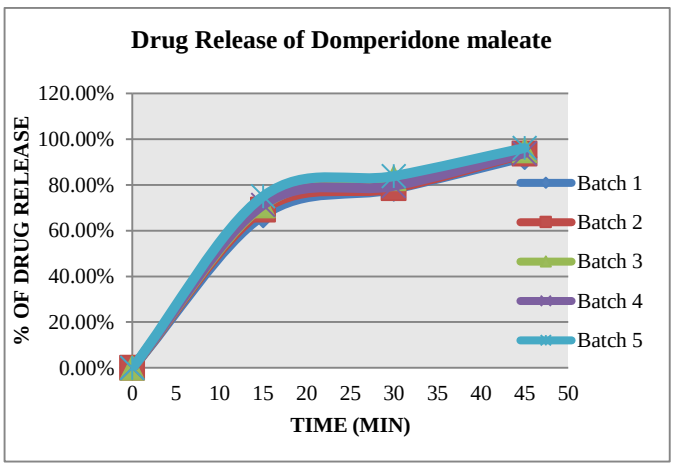


Fig 7

The use of superdisintegrants for preparation of fast dissolving tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared fast-dissolving tablet gets dispersed in the mouth quickly and releases the drug early as compared to its formulated conventional tablet.

Figure 4 show the cumulative percentage of Glibenclamide released from formulated tablet with different concentration of Starch. It is clear that the dissolution of Glibenclamide has improved considerably in formulation batch 5 as compared to formulation F1, F2, F3 and F4 and marketed preparation. F5 tablet showed good dissolution efficiency and rapid dissolution. The study shows that the dissolution rate of Glibenclamide can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants, which gives quick relief from emesis.

Result and Discussion

In the present study, Glibenclamide fast dissolving tablets were prepared by using, Microcrysytalline Cellulose (Avicel pH-200), starch and as superdisintegrants. A total number of 5 formulations were prepared by direct compression. The value of pre-compression parameters evaluated were within prescribed limits and indicated good flow property.

The data obtained of post compression parameters such as hardness, friability, weight variation, uniformity of content, thickness, disintegration time are shown above. The hardness was found to be in range of 2 to 3 kg/cm2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the BP (British Pharmacopoeia) limits. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, superdisintegrants and excipients. The percentage drug content of all the tablets was found to be between (95 to 105) of Glibenclamide, all the formulations which was within the acceptable limits. The percentage drug release by each tablet in the In Vitro drug release studies were based on the mean content of the drug present in respective tablet. The result of in vitro disintegration of all the tablets were found to be within prescribed limit satisfies the criteria of Fast Dissolving Tablet. Overall the Fast Dissolving Tablets of Glibenclamide showed an average of more than 90 % drug release range at the end of 45 min which is as per BP specifications of 90-110 % and it was also observed that formulations 5 took shortest time to release the maximum amount of drug whereas the other formulations took more than 45 min to release the drug. Comparison with other formulations, 3 shows a better drug release of 95.09 % at the end of 45 minutes. Further the formulation 5 was compared with marketed formulation (GPL) and found to be superior in terms of dissolution profile.

Conclusion

Glyburide belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. Direct compression method can be considered as an important method for the formulation of fast dissolving tablets of Glibenclamide compare to wet and dry granulation method. The rank order for the best 3 formulations is B5> B3 > B4. Formulation B5 having starch as the superdisintegrant is the best formulation of all. Higher the concentration of the lubricating agent (Magnesium Stearate or Talc), higher will be the disintegration time. Formulation having the better superdisintegrant with higher concentration will have better in vitro disintegration time and dissolution along with lesser friability and weight variation. Thus, it may be concluded that the fast dissolving tablets of Glibenclamide can be successfully prepared and undoubtedly the availability of various technologies and manifold advantages of fast dissolving tablets will surely enhance patient compliance and its popularity in the near future.

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