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Effect of super disintegrating agents on imatinib tablets by *in vitro* drug release study using kinetic model

Rahamathullah M, M.Purusothaman, V.Palanivel*

Department of Pharmaceutics, Padmavathi College of pharmacy, Dharmapuri, Tamilnadu, India.

ABSTRACT

The major problem in Imatinib drug formulation is high half-life which mainly results delay in peak plasma concentration. The concept of formulating fast dissolving tablets by super disintegrates offers a suitable practical approach for faster disintegration and dissolution characteristics. Among the various method of preparations fast dissolving tablets were prepared by using super disintegrates like croscarmellose sodium, cross povidone, sodium starch glycol ate by direct compression. The prepared Imatinib tablets were evaluated for free compression parameters like angle of repose, bulk density, tapped density, carr's index and post compression parameters like hardness, friability and weight variation, drug content uniformity, disintegration time and *In-vitro* dissolution studies. Among various fast dissolving tablets of Imatinib, F9 formulation shows maximum drug release of 30min (100.3%). The tablets of different formulations were subjected to various evaluations tests such as Hardness, Friability, and uniformity of weight, drug content and in vitro – dissolution. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets above 324mg is ±10%. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage batches of drug content were more than 98%. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacopoeia limit specifications for weight variation, drug content, hardness and friability.

Keywords: Imatinib, super disintegrating, kinetic model, cross povidone

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades' treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Eventoday these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to releasethe active principle immediately after oral administration to obtain rapid and complete systemic drug absorption. Drug absorption is defined as the process of movement of unchanged drug from the site ofadministration to systemic circulation[1]. Systemic drug absorption from a drug product consists of a succession of rateprocess for solid oral, immediate release drug products. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate israpid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step[2]. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely notleast, to improve the apparent solubility of the

Author for Correspondence:
V.Palanivel
Department of Pharmaceutics, Padmavathi College of pharmacy, Dharmapuri, Tamilnadu, India.

drug under physiologically relevant conditions.

Various approaches to improve the solubility or to increase the available surface area for dissolution include[3]

Micronization

The effective surface area of the drug is increased enormously by a reduction in the particlesize. Particle size and particle size distribution studies are important for drugs that have low water solubility. Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size decreased by milling to a micronized form has improvedthe oral absorption of the drugs, smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles and increases the dissolutionrate[4].

Modification of the crystal habit

The crystal form of drug is important variable in the present pharmaceutical processing. Therefore, they may exhibit different physico-chemical properties such as dissolution rate, powder flow and compressibility which is of pharmaceutical interest can differ for different habits of the same drug. In paracetamol, hexamethyl melamine and nitrofurantoin there is a modification of crystal habit which is useful to increase the oral absorption of drugs[5].

Polymorphism

It refers to the arrangement of a drug in various crystal forms or polymorphs. Polymorphs have same chemical structure but different physical properties such as solubility, density, hardness and compression characteristics. As a rule, for a drug that which exists in multiple polymorphic forms, the polymorph with the highest oral crystalline is the most stable form i.e., with the least amount of free energy, and consequently posses the highest melting point and the least solubility. Amorphous or metastable forms of drugs possessing high free energy can be forcibly created by controlling the crystallization process. They offer the advantage of high solubility. For example, □-form of chloramphenicol suspension is more soluble and better absorbed. So, polymorphism is a way to increase the solubility of poorly soluble drugs[6].

Pseudo polymorphism

Solubility of a poorly soluble drug is increased by Pseudo-polymorphism. The crystalline form of a drug can either be a polymorph or molecular adduct or both. The stoichiometric typeof adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates and the trapped solvent as solvent of crystallization. The solvates can exist in different crystalline forms called as pseudo polymorphs. This phenomenon is known as Pseudo polymorphism. When the solvent in associated with the drug is water, the solvate isknown as a hydrate. Hydrates are most common solvate forms of drugs.

Anhydrous form of a drug has greater aqueous solubility than the hydrates. For example, anhydrous form of theophylline and ampicillin have higher aqueous solubilities, dissolve at a faster rate show better bioavailability in comparison to their monohydrate and trihydrate formsrespectively[7].

Complexation/ Solubilization

These are approaches to increase the solubility of the drug. Solubilizing excipients in the formof pH adjusters, co-solvent and surfactants can significantly improve the solubility and dissolution of poorly water soluble drugs. pH adjustment depends on the pKa of the drugs generally regarded as safe buffering agents are used as necessary. pH ranges from 2 to 11 aregenerally acceptable for oral products, where as it is desirable to formulate as close to the physiological pH as possible for parental products.

In the co-solvent approach, a poorly soluble drug is mixed with a water miscible organic solvent, in which the drug has high solubility before addition to an aqueous medium. The solubility of a non-polar drug has generally been observed to increase in a log-linear fashion with the addition of co-solvent. The concepts of dielectric constant, solubility parameter and hydrogen bonding have been used to explain the phenomenon of co-solvency. The most commonly used co-solvents are ethanol, propylene glycol, glycine and low molecular weightpolyethylene glycols.

Inclusion complexes

Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drugs and excipients together resulting in enhanced solubilisation. The drug molecule resides insides the structure and is protected from unfavorable environments. Cyclodextrins don't increase the permeability of drugs in fact; formulation with cyclodextrins can reduce permeability. Hydrophilic cyclodextrins are non toxic in normal doses while lipophilic ones may be toxic. Hence methyl, hydroxylpropyl, sulfoalkyated and sulfated derivatives of natural cyclodextrinsthat posses improved aqueous solubility are preferred for pharmaceutical use.

Novel nanotechnologies for solubilisation include

i.) Nanocrystal technology uses a proprietary wet milling (also known as pearl milling) technique where the drug nanocrystal particles are sterically stabilized against agglomeration by surface adsorption of stabilizers. Polyvinyl pyrolidone, casein, glycerol polyethylene glycol and polyvinyl alcohol are examples of steric stabilizers to inhibit crystal growth[8].

ii.) Spray freezing into liquid technique involves the atomization of drug is incorporatedin a fluid medium directly into cryogenic liquids such as liquid nitrogen. The frozen particlesare lyophilized to obtain highly porous and dry free flowing particles.

METHODOLOGY

Materials

Imatinib, Crospovidone, Croscarmellose sodium, PVP K 30, Sodium starch glycolate, Magnesium Stearate, Talc, Mannitol.

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Compatibility studies

One of the requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Imatinib with Crospovidone, Sodium starch glycolate, Croscarmellose sodium. To study the compatibility of various formulation excipients with Imatinib, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and stored in air tight containers at 30 $\pm 2^0$c/65±5%RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR).[9-14]

RESULTS

In order to achieve the development of anti-cancer dosage forms, Imatinib was used as a model drug for the therapy of cancer, which was formulated by direct compression method employing different concentrations of fast disintegrating agents for fast release of drug, talc as diluent's and magnesium stearate as lubricant. In the present study Nine formulations (F1-F9) with variable concentrations of fast disintegrating agents (croscarmellose sodium, crospovidone, sodium starch glycolate) were prepared and evaluated for various physico-chemicals parameters, and In-vitro drug release studies. On the basis of In-vitro release studies the best formulation (F9) was selected. To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and Korsmeyer equation / Peppa's model equations along with zero order (cumulative amount of drug released verses time).

Evaluation of blend characteristics of fast disintegrating tablets of Imatinib

The blended granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, Hauser's ratio and drug content uniformity. The results of these evaluations are as follows:-

1. Angle of repose

Angle of repose ranged from 28° 00"± 1.1868 to 29°65"±1.837. The results were found to be below 30^0 and hence the blend was found to have good flow property. (Table-1).

2. Bulk density and tapped density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.3969± 0.004 to 0.4150±0.004 and 0.4652±0.007 to 0.4832± 0.006 respectively. (Table -2).

3. Compressibility index (Carr's index)

The compressibility index (%) ranged from 13.763± 0.861to 14.922± 1.145(Table -2). The blend was found to have free flowing property as the result were found to be below 18%.

4. Hauser's Ratio

The Hauser ratio ranged from 1.160± 0.011to 1.176± 0.016 (Table - 2). The result indicates the free flowing properties of the granules.

Table 1: Angle of repose for blend of Imatinib formulations

S.NO	Formulation Code	Height (h) (Cms)	Radius (r) (Cms)	h/radius	$\theta^* = \tan^{-1}$ h/r
1	F1	1.38± 0.0836	2.59± 0.0480	0.5324± 0.0421	28.005± 1.1868
2	F2	1.44± 0.0547	2.59± 0.0518	0.5565± 0.0319	29.095± 1.3901
3	F3	1.52± 0.0836	2.74± 0.0285	0.5550± 0.0359	29.031± 1.5818
4	F4	1.40± 0.0707	2.63± 0.0480	0.5328± 0.0359	28.030± 1.6043
5	F5	1.52± 0.0836	2.67± 0.0570	0.5699± 0.0422	29.654± 1.8371
6	F6	1.52± 0.0836	2.70± 0.0395	0.5634± 0.0387	29.374± 1.6930
7	F7	1.42± 0.0636	2.60± 0.0260	0.5461±0.0415	28.639±1.5480
8	F8	1.46± 0.0570	2.64± 0.0812	0.5530±0.0312	29.942±1.6250
9	F9	1.50±0.0838	2.67±0.0127	0.5617±0.0349	29.322±1.8795

*All values are expressed as mean ± S.D, n= 3

Table 2: Evaluation of properties of the blended powder for formulations of Imatinib

S.No	Formulation Code	Volume before tapping (V_o) ml	Volume after tapping (V) ml	Loose Bulk Density	Tapped Bulk Density	Carr's index	Hauser's Ratio
1.	**F1**	48.2± 0.447	41.4± 0.547	0.4150±0.004	0.4832± 0.006	14.107± 0.908	1.164± 0.012
2.	**F2**	48.8± 0.447	41.6± 0.547	0.4099± 0.003	0.4808± 0.006	14.753± 0.889	1.173± 0.012

3.	**F3**	49.4± 0.547	42.6± 0.547	0.4049± 0.004	0.4695± 0.006	13.763± 0.861	1.160± 0.011
4.	**F4**	49.6± 0.547	42.2± 0.836	0.4033± 0.004	0.4740± 0.009	14..922±1.145	1.176± 0.016
5.	**F5**	50.0± 0.707	42.6± 0.547	0.4001± 0.005	0.4695± 0.006	14.794± 0.971	1.174± 0.013
6.	**F6**	50.4± 0.547	43.0± 0.707	0.3969± 0.004	0.4652±0.007	14..682±1.071	1.172± 0.015
7	**F7**	48.6± 0.520	41.8± 0.472	0.4210± 0.002	0.4635± 0.004	14.742±0.704	1.172± 0.012
8	**F8**	49.2±0.602	42.6±0.836	0.4110±0.003	0.4601±0.003	14.671±0.871	1.168± 0.016
9	**F9**	50.1±0.447	44.0±0.547	0.4001±0.004	0.4580±0.004	14.528±1.124	1.170± 0.014

* All values are expressed as mean ± S.D, n= 3

Physical evaluation of oral fast disintegrating tablets of Imatinib

Imatinib fast disintegrating tablets were evaluated for various physical parameters namely– Hardness, Weight variation, Friability, Drug Content uniformity test etc.

1. Hardness test

The hardness of all batches ranged from 4.5-6.5 Kg/cm^2 (Table 3).

2. Friability test

The percentage friability of all batches ranged from 0.047 % to 0.094 % (Table 4).

3. Weight variation test

The percentage weight variations for all formulations are present in table- 17. All the formulations (F1-F9) passed weight variation test as per the Pharmacopoeias limits of 5%. (Table 5).

4. Drug content uniformity

Drug content was found to be uniform among the all formulations and ranged from 99.234±0.463 to 99.530±0.410 (Table 6).

Table 3: Physical evaluation of fast disintegrating tablets of Imatinib Hardness (kg/cm^2)

S. No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	4.5	6.5	5.0	5.5	4.5	6.0	5.5	6.0	4.5
2.	5.0	6.5	6.0	6.0	5.0	6.5	5.0	5.5	5.5
3.	6.5	5.0	5.5	5.5	5.0	5.5	6.0	6.0	4.5
4.	6.5	4.5	5.0	6.0	5.5	5.0	6.5	5.5	5.5
5.	6.5	5.0	5.5	4.5	6.0	5.0	6.5	5.5	5.5
Avg.	**5.8**	**5.5**	**5.4**	**5.5**	**5.2**	**5.6**	**5.8**	**5.7**	**5.1**

Table 4: Friability test for fast disintegrating Imatinib tablets

Formulation Code	Weight of 6 tablets before test (gms)	Weight of 6 tablets after test (gms)	Friability $F = 100(1-w_0/ w_t)$
F1	3.017	3.011	0.120 %
F2	3.011	3.009	0.066 %
F3	2.999	2.995222	0.133 %
F4	3.015	3.011	0.132 %
F5	3.012	3.007	0.166 %
F6	3.014	3.007	0.232 %
F7	3.015	2.950	0.110 %
F8	3.090	3.150	0.125 %
F9	3.010	3.015	0.130 %

Table 5: Weight variation test for fast disintegrating tablets of Imatinib

S. No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	510	505	510	510	490	510	505	500	510
2.	510	510	510	490	500	500	520	490	480
3.	510	510	510	510	500	510	510	505	510
4.	490	480	490	510	490	490	480	490	490
5.	510	410	520	510	510	510	500	505	500
6.	480	410	520	500	480	520	490	480	480
7.	510	500	490	500	500	510	500	500	510
8.	520	490	520	510	510	520	500	510	500
9.	510	510	500	500	500	500	505	480	490
10.	510	510	520	510	500	510	510	500	510
11.	510	490	510	510	500	500	510	480	490
12.	500	510	510	520	520	510	510	500	500
13.	510	500	510	510	510	520	510	500	510
14.	490	500	490	510	500	510	510	500	510
15.	510	510	510	510	510	510	520	500	500
16.	500	500	500	500	510	500	505	500	510

17.	510	510	510	510	480	510	520	500	510
18.	500	510	500	510	520	500	505	490	490
19.	520	490	520	500	510	510	510	490	500
20.	510	510	510	510	500	510	520	505	505
Average weight	505.5	502.5	508.0	507.0	502.0	508.0	506.0	508.2	5108.2
% Maximum Positive deviation	4.90	2.56	4.02	4.3	6.16	4.02	4.60	4.54	3.55
% Minimum Negative deviation	5.24	7.69	9.3	4.7	7.13	2.68	2.26	2.34	1.33

Table 6: Content uniformity for Imatinib fast disintegrating tablets

S. No.	Formulation Code	Standard absorbance	Sample absorbance	Working standard weight (mg)	% Drug Content * ± S.D.
1.	F1	0.3657	0.3532	100	96.58
2.	F2	0.3657	0.3567		97.50
3.	F3	0.3657	0.3593		98.24
4.	F4	0.3657	0.3579		97.86
5.	F5	0.3657	0.3627		99.17
6.	F6	0.3657	0.3553		97.15
7.	F7	0.3657	0.3612		98.70
8.	F8	0.3657	0.3632		99.30
9.	F9	0.3657	0.3602		98.40

In -vitro drug release for fast disintegrating tablets of Imatinib

The fast disintegrating tablets were prepared and evaluated on trial basis. Total nine formulations (F1-F9) prepared by using croscarmellose sodium, crospovidone, sodium starch glycolate. The release of Imatinib from the fast disintegrating tablet was studied in 900 ml of 0.1 N Hcl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37° ± 0.5° C. Drug content was determined by UV-visible spectro-photometer at 285 nm. Dissolution studies were performed for30 min. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

DISCUSSION

Imatinib is one of the first cancer therapies that has shown a potential for a novel approach in cancer treatment. Imatinib represents a therapeutic breakthrough as a targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) specifically BCR-ABL, c-KIT, PDGFRA. It has become the first line drug in management of several cancers. Conventional formulation of Imatinib is administered single time a day (100 to 400 mg daily) because of its high half-life ($t_{1/2}$ = 18-40 hrs.). with all evident advantages proved to be suitable candidates for development of a fast dissolving dosage form. In the present study, developing a oral fast dissolving dosage form of Imatinib an anti-Cancer drug with using super disintegrating agents (crospovidone, croscarmellose sodium and sodium starch glycolate). Hence in the present work, an attempt has been made to formulate the fast dissolving tablets of Imatinib using 3 different types of fast dissolving agents with different ratios such as (5mg, 7.5mg, 10mg).

Characterization of Bulk Drug and Effect of various formulation Excipients

FT-IR spectra of pure Imatinib and its physical mixtures (1:1 ratio w/wt) with the excipients used in this study. The characteristic peak of carbonyl group at 1680-1740 cm^{-1}, NH_2 group at 3200-3400 cm^{-1} and hydroxyl group at 3300-3500 cm^{-1} present in the entire spectrum indicates the stable structure of Imatinib in the solid admixtures.

Physical properties of Granules

The granules for the tablet preparation were prepared to the formula. The granules of different formulations were evaluated for angle of repose, LBD, TBD, Compressibility index, Hauser's factor and drug content. The results of angle of repose range from 28.005 to 29.942 indicate good flow properties of the granules. This was further supported by lower compressibility index values. Generally, compressibility index values from 14.10 to 14.92 (up to 16%) result in good to excellent flow properties. The Hauser's ratio of granules of all formulations was <1.2 indicates free flowing. The drug content in the weighed amount of granules of all formulations was found to be uniform. Other parameter, such as bulk density, tapped density was found to be within acceptable limits (Table 14). All these results indicate that the granules possessed satisfactory flow-properties, compressibility and drug-content. Finally, both fast disintegrating level and fast disintegrating type did not affect the physical properties of the prepared granules.

Physical properties of Tablets

The tablets of different formulations were subjected to various evaluations tests such as Hardness, Friability, and uniformity of weight, drug content and in vitro – dissolution. In a weight variation test, the pharmacopoeia

limit for the percentage deviation for tablets above 324mg is ±10%. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage batches of drug content were more than 98%. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacopoeia limit specifications for weight variation, drug content, hardness and friability.

In-vitro Release Studies

The in vitro drug release characteristics were studied in 900ml of 0.1NHcl for 30min, using USP. XXIII Dissolution apparatus type II (paddle) method. The results of dissolution studies indicate that F1, F2, F3 released 92%, 96%, and 97% of Imatinib at the end of 30 min. Formulation F1, F2, F3 formulated with crospovidone by gradual increasing the ratio of crospovidone (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of wicking. The results of dissolution studies indicate that F4, F5, F6 released 94%, 95%, and 97% of Imatinib at the end of 30 min. Formulation F4, F5, F6 formulated with croscarmellose sodium by gradual increasing the ratio of croscarmellose sodium (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of minimum of gelling and wicking due to fibrous structure.

The results of dissolution studies indicate that F7, F8, F9 released 96%, 99%, and 100.3% of Imatinib at the end of 30 min. Formulation F7, F8, F9 formulated with sodium starch glycolate by gradual increasing the ratio of sodium starch glycolate (5mg, 7.5mg, 10mg) shows increasing in drug release at the end of 30min by using mechanism of rapid and extensive swelling with minimum gelling. To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and korsmeyer equation/ peppa's model equation along with zero order release pattern, the release rate kinetic data for all the other equations. The formulations F1-F9 showed higher Regression values for first order plots indicating that drug release followed first order kinetics. The in vitro release profiles of drug from all the formulations could be best expressed by Higuch's equation, as the plots showed high linearity Regression 0.7945 to 0.9259. To confirm the diffusion mechanism, the data were fit into korsmeyer, equation, with slope (n) values ranging from 0.2132 to 0.3413. This indicates that the release of drug follows Fickian transport. It means in release of drug from the tablet dissolution and diffusion both mechanisms are used.

CONCLUSION

It is evident from the result of formulation F9 which is formulated with sodium starch glycolate (10mg) shows maximum and better release at the end of 30min, when comparatively with F1-F8. This may be due to their rapid swelling mechanism, less particle size, and also the cost of sodium starch glycolate is less when compared to crospovidone, croscarmellose sodium. Thus the work proves that sodium starch glycolate is better super disintegrating agent in the In-vitro drug release and it is cost effective. The formulation F1-F9 exhibited fickian drug release mechanism.

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