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Incompatibility of Bisoprolol Fumarate with Some Super-disintegrating Agents

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAMS, MJH and RK designed the study and performed the analyses of the study. Authors RK and MZS performed the DSC tests, wrote the protocol and first draft of the manuscript. Author AR managed the literature searches and review process. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Bisoprolol fumarate, a selective $\beta_1$adrenoreceptor blocker, is usually formulated as immediate release tablet dosage form. While developing the immediate release tablet formula in laboratory, the assay and dissolution results were found below acceptance limit in some formulation. The formulations differed only in disintegrating agents. Therefore a chemical interaction was suspected with some of the disintegrants with the drug used in the formulas. The aims of this study were to find out the interaction with the specific excipient.
Study Design: Consequently, a pilot study of binary mixture of Bisoprolol-excipients (conventionally used in solid dosage form, e.g. binder, diluents, disintegrating agents, glidants, dissolution enhancer etc.) was carried out in laboratory using different analytical methods such as dissolution tester, UV, HPLC, DSC etc. Also formulated tablets were studied.

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Place: Study was carried in drug testing and analytical research laboratory in Center for Advanced Research in Sciences, University of Dhaka.
Results: From the study, bisoprolol fumarate was found quite incompatible with 'sodium starch glycolate'(SSG) and 'croscarmellose sodium'(CCS) both of which are used as disintegrating agents in conventional solid dosage forms. But other disintegrating agents such as kollidon CL (KCL) has shown no interaction towards bisoprolol fumarate.
Conclusion: Thus from this study we reached a valuable conclusion that bisoprolol fumarate is quite incompatible with two disintegrating agents namely sodium starch glycolate and croscarmellose sodium. With sodium starch glycolate, the drug was found to be degraded by around 19% whereas with croscarmellose sodium degradation was estimated around 13% in freshly prepared tablets. On the other hand, kollidon CL is compatible with this drug in its solid dosage formulation.

Keywords: Bisoprolol fumarate; incompatibility; sodium starch glycolate; croscarmellose sodium; kollidon CL; HPLC; DSC.

1. INTRODUCTION

Pharmaceutical excipients are part and parcel in the formulation of any type of dosage form [1]. Although excipients are defined as pharmacologically, chemically and physically inert substances, still these can sometimes undergo significant physical and/or chemical interaction with active drug [2]. Study of drug-excipient interaction is, therefore, an utmost important factor in pre-formulation phase of a drug dosage form, because any type of physical or chemical interaction between active drug and excipients can alter stability, dissolution and bioavailability of the drug which ultimately affects its safety and/or efficacy [3]. The successful formulation of a stable and effective solid dosage form largely depends on the careful choice of the excipients. The pharmaceutical development of solid dosage form should, therefore, imply a previous pre-formulation study of the drug and excipients compatibilities [4]. A number of experimental techniques (i.e. DSC, IR, X-ray powder diffraction, Scanning Electron Microscopy, HPLC etc.) are used to investigate the interaction between drug and excipients [5,6]. Analyses done by these techniques can provide valuable information of any physical or chemical interaction between drug molecules and excipients and thus any potential instability problem of drug molecule in the final solid or liquid dosage formulation can be sorted out.

The aim of present study was to prepare immediate release tablet formulations of bisoprolol fumarate and determine the possible interactions of bisoprolol fumarate with the commonly used disintegrating agents in solid dosage like sodium starch glycolate (SSG), croscarmellose sodium (CCS) and kollidon CL (KCL). Tablet formulations were also investigated to show the effect of drug-excipient interactions by dissolution study, DSC and HPLC analyses.

Pharmacologically, bisoprolol fumarate is a selective $\beta_1$adrenoreceptor blocker. It is widely used in hypertension and angina pectoris [7]. Chemically bisoprolol fumarate is (*RS*)-1-{4-[(2-isopropoxyethoxy) methyl]phenoxy}-3-(isopropylamino) propan-2-ol hemifumarate [8].

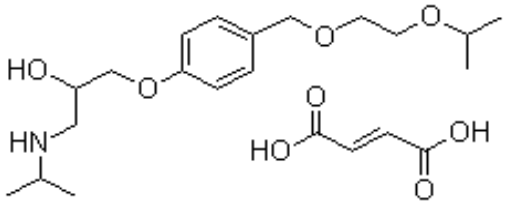

Fig. 1. Structure of Bisoprolol Fumarate

Croscarmellose sodium (CCS) is a sodium salt of a polycarboxymethyl ether of cellulose. Sodium starch glycolate (SSG) is a sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch [9,a]. Kollidon CL or polyvinylpyrrolidone (KCL) is a cross-linked homopolymer of *N*-vinyl-2-pyrrolidon [10]. These all three disintegrating agents are water insoluble polymers and they disintegrate by swelling in contact with water [11-13].

To the best of our knowledge, there is no report published, about incompatibilities of bisoprolol fumarate with any excipients, neither in any journal nor in any textbook.

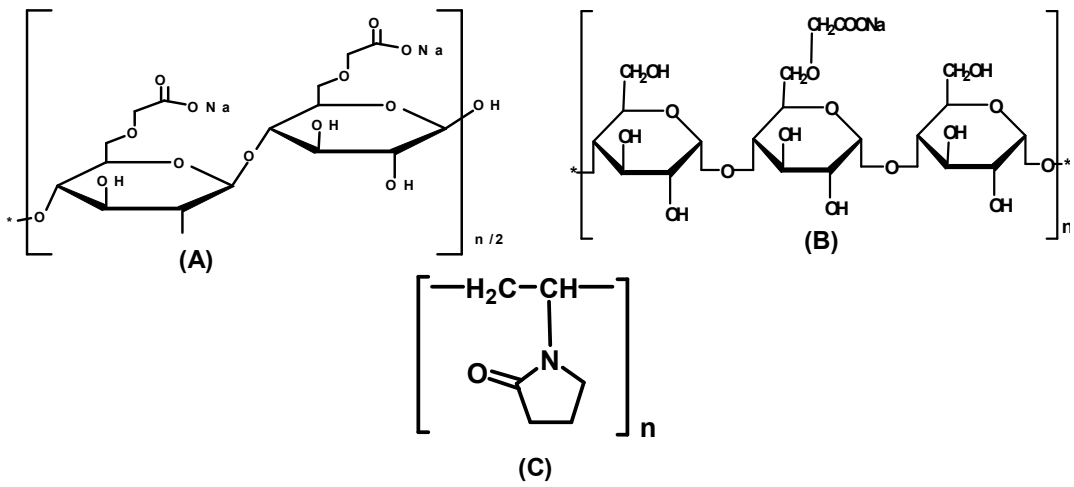

Fig. 2. Croscarmellose sodium (A), Sodium starch glycolate (B) and Kollidon CL (C)

2. MATERIALS AND METHODS

2.1 Materials

All the excipients were purchased from local market. Working standard of bisoprolol fumarate with potency of 99.3% was a kind gift from ACI Pharmaceutical Ltd., Bangladesh.

2.2 Instrumentation

Dissolution tester (model: UDT-804; Logan Instruments Corporation, USA), Differential Scanning Calorimeter (model: DSC-60W, Shimadzu, Japan) and High Performance Liquid Chromatographic System (Shimadzu-UFLC Prominence), equipped with an auto sampler (Model- SIL 20AC HT) and UV-Visible detector (Model-SPD 20A) were used for the analyses. The HPLC data was recorded using LC-solutions software. Accelerated stability test chamber (CLC 404 Climacell, Germany) was used to run the pre-formulation study of binary mixture of bisoprolol fumarate and excipients.

2.3 Pre-formulation Study

Bisoprolol fumarate was mixed well with all excipients individually at a ratio of 1:1 w/w and was placed in small vials. These vials (closed mouth) were kept for observation in ambient condition and in stability chamber (40 °C and of 75% Relative Humidity). Visual observation was carried out at initial stage and after 3 months. The samples were also assayed by HPLC.

2.4 Formulation Method of Tablet

In order to assess the bisoprolol fumarate - excipients interaction in solid dosage form, three different formulations F1, F2 and F3 were prepared with three different disintegrating agents as SSG, CCS and KCL, respectively which are shown in the Table 1.

Table 1. Three different tablet formulation containing 5 mg bisoprolol fumarate

Formulation code	Drug (5.0 mg)	Binder (7.0 mg)	Disintegrating agent (5.0 mg)	Dissolution enhancer (8.0 mg)	Diluent (73.0 mg)	Lubricant (0.75 mg)	Glidant (1.25 mg)
F 1	Bisoprolol fumarate	Starch-1500	SSG	Lactose monohydrate	Avicel PH 102	Magnesium stearate	Colloidal silicon dioxide
F 2	Bisoprolol fumarate	Starch-1500	CCS	Lactose monohydrate	Avicel PH 102	Magnesium stearate	Colloidal silicon dioxide
F3	Bisoprolol fumarate	Starch-1500	KCL	Lactose monohydrate	Avicel PH 102	Magnesium stearate	Colloidal silicon dioxide

Active material (bisoprolol fumarate), binder (starch 1500), one of the three disintegrating agents (SSG/CCS/KCL), dissolution enhancer (lactose monohydrate) and diluent-microcrystalline cellulose (avicel PH 102) were mixed well.

Then lubrication was achieved with lubricating agent (magnesium stearate) and glidant-colloidal silicon dioxide (aerosil-200). Then these mixed materials were compressed as tablet containing 5 mg of bisoprolol fumarate and analyzed to observe dissolution and assay of these three unique formulations.

2.5 Analytical Methods

2.5.1 Identification of drug

The identity of the drug was determined by DSC and HPLC. The DCS of drug was done to get the endothermic peak corresponding to its melting point. The HPLC analysis of the drug was done as per the method described in United States Pharmacopeia (USP-35, NF-30, volume-II).

2.5.2 Assay of Bisoprolol Fumarate

Determination of bisoprolol fumarate in the freshly prepared tablets made by the formula as stated above (F1, F2 and F3) was performed by HPLC according to the method described in USP [9,b]. The analysis was carried out C_8 column (150 mm× 4.6 mm, 5 µm particle size, Phenomenex Inc.)

2.5.3 *In vitro* dissolution study

The dissolution study of the freshly prepared tablets made by the formula as stated above (F1, F2 and F3) was performed using USP Apparatus 2 (paddle) at 75 rpm for 20 minutes. Percent release was determined by HPLC chromate-graphic method as described in USP [9,b].

2.5.4 Compatibility study by DSC

A differential scanning calorimetry was used to study the thermal analysis of drug-excipient compatibility. Firstly, binary mixtures of bisoprolol fumarate and excipients were prepared in 1:1 w/w ratio. The drug-excipient mixture was scanned in the temperature range of 30-150ºC under nitrogen atmosphere. The heating rate was 10ºC per min and the obtained thermograms were reviewed for evidence of any type of interaction.

3. RESULTS AND DISCUSSION

3.1 Identification of Bisoprolol Fumarate

The identity of drug was assessed by both HPLC and DSC. The HPLC method was selective since there was no other peak due to any degradation products or excipients or impurity in the formulation on the same retention time of bisoprolol fumarate (4.5 ± 0.1 minute in current analysis) (Fig. 3). The DSC thermogram of bisoprolol fumarate showed a sharp endothermic peak at 101.39ºC corresponding to its melting point (Fig. 4).

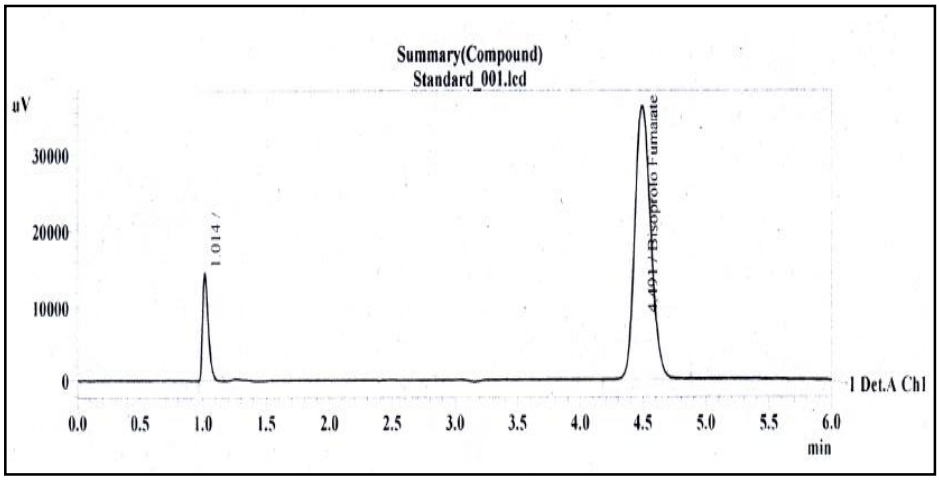

Fig. 3. HPLC chromatogram of standard Bisoprolol Fumarate

3.2 Pre-formulation Study

Physical mixtures of drug-excipients were examined initially and after 3 months to check any physical change in naked eye. At initial stage, it was found that there was no change in any binary mixture and all the mixtures were free following powder. After 3 months, bisoprolol fumarate formed mild to moderate lump with CCS in stability chamber. With SSG, the lump formation was so significant and severe that it was easily viewed in naked eye and the whole mass stuck to the bottom of the glass vial (Fig. 5). This physical change indicated some sort of interaction of those excipients with this drug. Results were summarized in Table 2.

3.3 In vitro Dissolution Study

Initially, formulated tablets of three different formulations with variation in disintegrating agents were taken to study their dissolution. Though tablet formulation F1 and F2 (containing SSG and CCS) showed lower dissolution rate (84% and 77%, respectively), still we could not assure presence of any chemical interaction because dissolution is often retarded due to various physical factor such as hydrophobicity of drug or excipients etc. Results were shown in Tables 3-5.

3.4 Assay of Bisoprolol Fumarate in Three Different Formulations

Tablets from three formulations were assessed to find out the bisoprolol fumarate content in each tablet formulation according to the USP guideline. In case of F1, average recovered concentration was found 4.01 mg which was 20% lower than the claimed amount. In case of F2, average recovered concentration was 4.32 mg which was 14% lower the claimed amount. On the other hand for F3, average recovered concentration was 4.99 mg which was around 99.8% of the claimed amount. This assay result strongly indicated a chemical reaction of bisoprolol fumarate with SSG and CCS. But unfortunately no degradation peaks were detected in the chromatogram. This may due to be the fact that either the degraded products were not retained in the column at all or more preferably those were not detectable at the method's absorbance maxima. The assay results are summarized in Table 6.

For further investigation, binary mixture of bisoprolol fumarate and individual excipients were assessed on HPLC and compared with that of freshly prepared standard solution. It was found that peak area and heights were retained same with each excipients but with SSG and CCS significant changes were noted. The results were shown in Table 7.

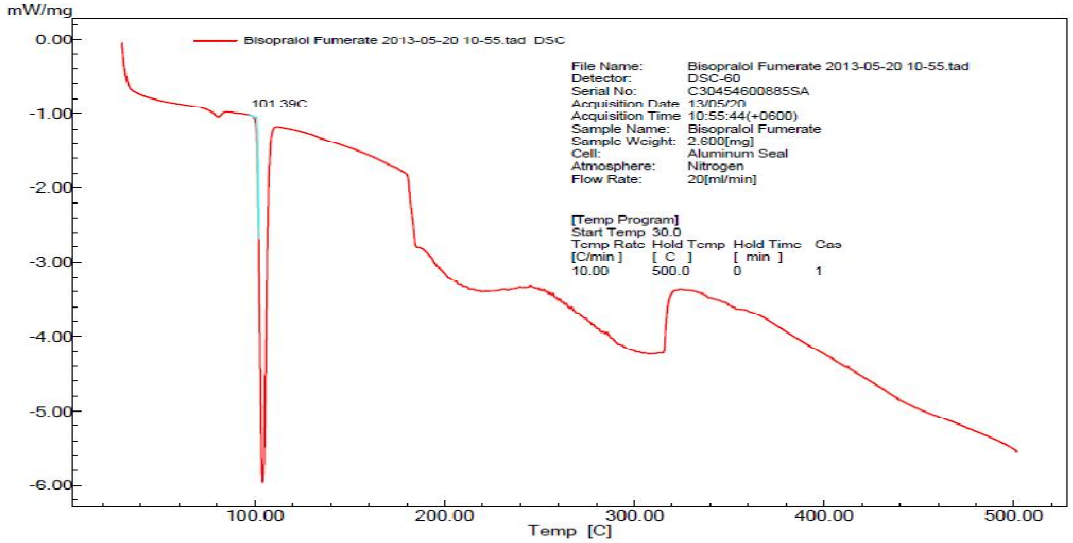

Fig. 4. DSC thermogram of standard Bisoprolol Fumarate

Table 2. Findings of pre-formulation studies

Physical mixtures	Observation	
	Ambient	40°C + 75% RH
Bisoprolol fumarate + lactose monohyrate	No change	No change
Bisoprolol fumarate + avicel PH-102	No change	No change
Bisoprolol fumarate + sodium starch glycolate	Significant lump formation	Hard and sticky lump formation
Bisoprolol fumarate + cross carmellose sodium	Small lump formation	Small lump formation
Bisoprolol fumarate + kolidon CL	No change	No change
Bisoprolol fumarate + maize starch	No change	No change
Bisoprolol fumarate + magnesium stearate	No change	No change
Bisoprolol fumarate + aerosil-200	No change	No change

Table 3. Dissolution from formulation F1

Sample	Theoretical Plate	Area	Height	Conc. in %
S-01	4799.77	88523	7901	75.73
S-02	4809.11	88661	7904	75.84
S-03	4763.62	89692	7991	76.41
S-04	4757.39	89715	7998	76.43
S-05	4728.02	93649	8355	79.89
S-06	4747.52	93541	8378	79.79
Average	4767.57	90630	8088	77.35

Table 4. Dissolution from formulation F2

Sample	Theoretical Plate	Area	Height	Conc. in %
S-01	5329.02	100706	8921	85.79
S-02	4838.41	101740	8890	86.67
S-03	4838.41	101740	8890	86.31
S-04	5361.47	99245	8891	84.19
S-05	4640.99	99322	8444	84.73
S-06	4738.13	95387	8498	81.37
Average	4957.74	99690	8756	84.84

3.5 DSC Analysis of Bisoprolol Fumarate-Excipients Interaction

All those findings in HPLC analyses could be evident enough to indicate incompatibility of bisoprolol fumarate with SSG and CCS; however, DSC tests of the pure bisoprolol fumarate and binary mixtures with excipients were carried out because DSC has become unique in testing the presence of chemical interaction between drug and excipients. Consequently three disintegrating agents-SSG, CCS and KCL were chosen for DSC analysis to confirm the presence of any chemical interaction with the bisoprolol fumarate. From the DSC thermograms it was confirmed that there was a chemical interaction of bisoprolol fumarate with SSG and CCS, but KCL was found to be completely inert towards the drug.

DSC thermograms of pure drug and binary mixture of drug and disintegrating agents (1:1 w/w ratio) were shown in Fig. 6.

Table 5. Dissolution from formulation F3

Sample	Theoretical Plate	Area	Height	Concentration in %
Sam-01	5685.27	134845	9478	97.19
Sam-02	5784.06	144299	9998	104.00
Sam-03	6181.90	132954	9474	95.82
Sam-04	6123.76	130652	9664	94.17
Sam-05	6762.47	133768	9965	96.41
Sam-06	3659.29	111980	6495	97.89
Average	5699.45	131416	9179	97.58

Fig. 5. Physical state of binary mixture of Bisoprolol Fumarate with KCL, SSG and CCS after 3 months

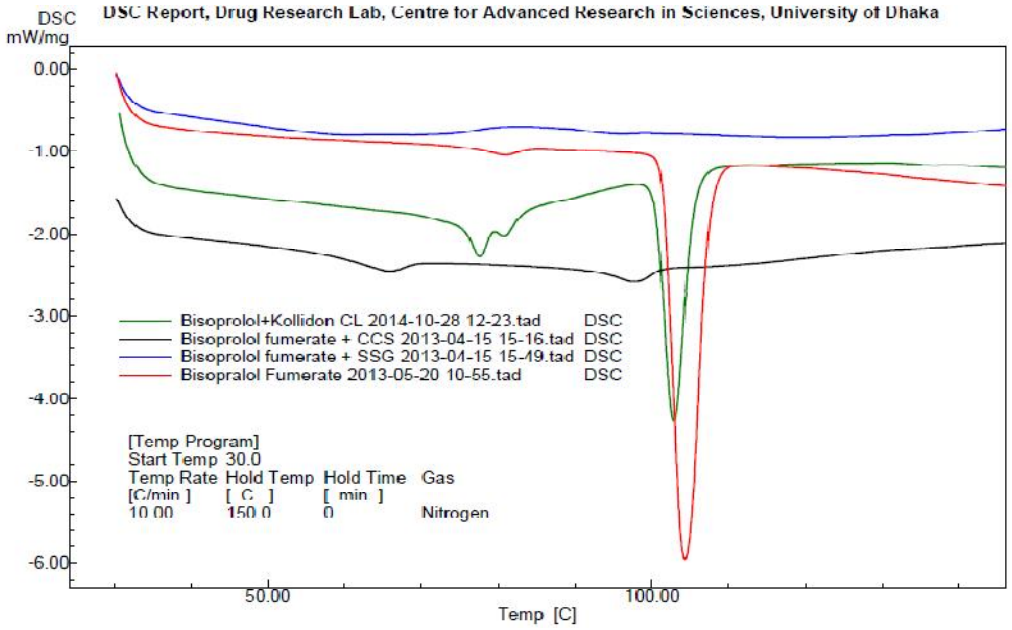

Fig. 6. DSC thermograms of Bisoprolol Fumarate and binary mixtures with disintegrating agents

Table 6. Assay result of Bisoprolol Fumarate in tablets

Formula No.	Disintegrating agent used	Average area	Average recovered concentration (mg/ tab)	Claimed amount (mg/ tab)	% Recovery	% Loss
F1	SSG	247902	4.01	5	80.02	19.98
F2	CCS	273955	4.32	5	86.40	13.6
F3	KCL	560735	4.99	5	99.80	0.2

Table 7. Assay of bisoprolol fumarate from binary mixture of excipients using HPLC after 3 months

Binary mixture of 'Active-excipients'	Area*	% of area change with respect to fresh standard	Height*	% of height change with respect to fresh standard
Bisoprolol fumarate (Freshly prepared)	424071	--	51205	--
Bisoprolol fumarate + lactose monohyrate	421744	Negligible	50852	Negligible
Bisoprolol fumarate + avicel PH-102	423547	Negligible	50876	Negligible
Bisoprolol fumarate + sodium starch glycolate	322547	23.9	42898	16.22
Bisoprolol fumarate + cross carmellose sodium	368809	13.03	44979	12.16
Bisoprolol fumarate + kolidonCl	423154	Negligible	50489	Negligible
Bisoprolol fumarate + maize starch	424617	Negligible	50521	Negligible
Bisoprolol fumarate + magnesium stearate	421546	Negligible	50425	Negligible
Bisoprolol fumarate + aerosil-200	422057	Negligible	51211	Negligible

**Mean of three runs*

The exact mechanism of degradation pathway of this drug with SSG or CCS has yet to be discovered. But some explanation can be stipulated depending upon the structures of drug. As the drug has amine group, the most possible reactions that can take place is the addition reaction between the amine group of drug and the hydroxyl group of SSG/CCS, or amide formation with carboxylate ion on SSG/CCS which can be mediated by heat produced during compression.

4. CONCLUSION

From the research work it was concluded that bisoprolol fumarate was incompatible with sodium starch glycolate and croscarmellose sodium in solid dosage formulations. But kollidon CL was found to be compatible as a disintegrating agent with bisoprolol fumarate for the formulation of orally fast disintegrating tablets. Therefore in conventional orally disintegrating tablets of this drug, kollidon CL should be used as disintegrant.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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