Formulation development and comparative *in vitro* study of metoprolol tartrate (IR) tablets

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Abstract: The objective of the present work was to develop Immediate Release (IR) tablets of Metoprolol Tartrate (MT) and to compare trial formulations to a reference product. Six formulations (F1-F6) were designed using central composite method and compared to a reference brand (A). Two marketed products (brands B and C) were also evaluated. F1-F6 were prepared with Avicel PH101 (filler), Crospovidone (disintegrant) and Magnesium Stearate (lubricant) by direct compression. Pharmacopoeial and non-pharmacopoeial methods were used to assess their quality. Furthermore, drug profiles were characterized using model dependent and independent (f_2) approaches. Brands B and C and F5 and F6 did not qualify the tests for content uniformity. Moreover, brand B did not meet weight variation criteria and brand C did not satisfy requirements for single point dissolution test. Of the trial formulations, F2 failed the test for uniformity in thickness while F4 did not disintegrate within time limit. Only F1 and F3 met all quality parameters and were subjected to accelerated stability testing without significant alterations in their physicochemical characteristics. Based on AIC and $r^2_{adjusted}$ values obtained by applying various kinetic models, drug release was determined to most closely follow Hixson-Crowell cube root law. F1 was determined to be the optimized formulation.

Keywords: Metoprolol tart rate, direct compression, formulation development, kinetic models, comparative analysis.

INTRODUCTION

Tablet is the most preferred dosage form (Mahato and Narang, 2011, Shojaei, 1998). It offers the advantages of low production costs, precise dosages, increased physical and chemical stability, simplicity of preparation, convenient packaging, shipping and storage, and ease of administration (Lilja *et al*., 2008, Rudnic and Schwartz, 2006, Surbhi *et al*., 2012).

Based on the release characteristics of a drug from an oral dosage form, the USP defines two terms in solid dosage form technology, one of which is conventional or immediate release dosage forms. Immediate release (IR) tablets are designed to disintegrate and release their contents almost immediately after ingestion and do not contain any features such as coatings to control rate of release of active pharmaceutical ingredient (API)(Madan, 2010). Consequently, drug dissolution is faster (depending on solubility of drug), absorption is quicker (subject to permeability of drug) and a more rapid onset of action is observed without the potential of dose dumping (Reddy *et al*., 2010).

The main aim of a dosage form is to achieve a predictable therapeutic response to an API included in the formulation which is capable of large scale manufacture with reproducible product quality. Product quality is reflected by numerous features such as uniformity of dose of drug, elegant and consistent tablet appearance that includes uniformity in tablet weight, size, and thickness in order to increase patient and prescriber acceptability and palatability. Moreover, the quality of dosage form also depends upon controlled and reproducible drug release that can be evaluated through dissolution tests. Similarly, the solid dosage form must have sufficient mechanical strength to withstand fracture and erosion during handling, transportation and use, provided that it disintegrates appropriately in compliance with pharmacopoeial limits. Furthermore, chemical, physical and microbiological stability must be ensured(O'Donnell and Bokser, 2006, Surbhi *et al*., 2012).

Uniformity of appearance is essential to maintain the confidence of the consumer. Homogeneity of content ensures the delivery of appropriate drug content. Non-uniformity may result from a variety of factors such as poor flow characteristics, improper mixing, size separation of the particles etc. It is therefore imperative that all formulation factors should be rigidly controlled (Rudnic and Schwartz, 2006). Dissolution profiles should be generated according to pharmacopoeial recommendations to determine drug release. Dissolution profiles can be analyzed to determine kinetics of drug release (Costa and Sousa Lobo, 2001) and, under certain conditions, to apply for biowaiver (FDA, 2000).

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Metoprolol tartrate (MT) is a β_1-adrenoceptor blocking agent. Most of its effects are due to occupancy and blockade of β adrenergic receptors (Rehsia and Dhalla, 2010). However, it also has a local anesthetic effect which is not caused by its β blocking action (Bankston and Kass, 2010) It is best indicated for angina, cardiac arrhythmia, hypertension and myocardial infarctions(Hoffman, 2004). It is a white or almost white crystalline powder that is very soluble in water, freely soluble in ethanol (96%)(BritishPharmacopoeia, 1998).

In the present study, the two generic brands of MT available commercially (designated brands B and C) in the Pakistani market were subjected to *in vitro* physicochemical evaluation i.e. hardness, thickness, weight, friability, disintegration time, single- and multi-point dissolution and assay. A further six formulations (F1-F6) were developed and tested, and their results were compared with the innovator's product (brand A). The aim of the research was to evaluate the quality of the marketed products and to design a cost effective formulation qualifying applicable pharmaceutical standards.

The trial formulations were prepared by direct compression (DC) method using Avicel PH 102 (diluent), Crospovidone (disintegrant) and magnesium stearate (lubricant). Tablet compression by DC is the simplest and cheapest means of producing tablets. In a survey of 58 pharmaceutical manufacturers conducted by Shangraw and Demarest in 1993, the single most common choice for tablet production was DC (Shangraw and Demarest, 1993).The main advantages are lower production time and cost, improved product stability, and tablet disintegration and hence, drug dissolution are generally fast (Aufmuth, 1996, Zheng and Ternick, 2009). It can be used for drugs that are water soluble (Dokala and Pallavi, 2013).

MATERIALS AND METHOD

Selection of brands

Marketed MT IR tablets were procured. The innovator's product was labeled Brand A. The two generic products available were labeled Brand B and C.

Chemicals and reagents

Standard Metoprolol Tartrate was donated by ATCO Laboratories Limited. Analytical grade hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate and absolute ethanol were purchased commercially. Distilled water was prepared in the lab using Distillation Assembly (Model number WSB/4, Serial number 234A, Hamilton Lab Glass Ltd., England).

Equipment and methods

Preparation of Tablets

Six different formulations (F1-F6) were prepared by direct compression method as per the formula given in table 1.

Tablet ingredients were accurately weighed using Sartorius Weighing Balance according to the formulations given in said table and passed through an 80 mesh sieve. Following geometric dilution principles, the ingredients were mixed in a poly bag of suitable size. Active ingredient MT was first mixed with Avicel PH 102 and Crospovidone for 5 minutes using tumbling action. Magnesium stearate was then added to the mixture and tumbling was resumed for a further 5 minutes. The whole mixture was sieved a second time using an 80 mesh sieve. Finally, the blend was compressed using Korsch Erweka single punch manual tablet machine with preset hardness and weight controls.

Pre-formulation evaluation

a) Carr's Index: The flow-ability of powder blend was determined by(Wells, 2002):

$$Carr's Index = \frac{TappedBulkDensity - PouredBulkDensity}{TappedBulkDensity} \times 100$$

Where,

$$TappedBulkDensity = {Weight of powder}/{True volume}$$

And,

$$PouredBulkDensity = {Weight of Powder}/{Bulk volume}$$

b) Angle of Repose: Further determination of flow-ability of powder blend was made using the fixed base approach to calculate angle of repose. The following formula was used (USP28-NF23, 2004a):

$$\theta = \tan^{-1}\frac{Height}{0.5Base}$$

The results obtained are given in table 2.

Physical evaluation of tablets

Various physical characteristics of the tablets were evaluated as per the official monographs obtained from BP and USP. The parameters tested include weight variation (Sartorius Ag Göttingen, CP 224S, Germany), hardness (Fujiwara Hardness Tester, Ogawa Seiki Co. Ltd., Japan), friability (Erweka GmbH D-63150, Type: TA-200, Germany), thickness (Digital Vernier Caliper, Shanghai ShenHan Measuring Tools Co. Ltd. GB/T14899-94, China) and disintegration (Erweka D-63150, Typ: ZT-502, Germany). The results are shown in table 3.

Assay and content uniformity

A random sample of 20 tablets of the test formulations of MT was assayed spectrophotometrically at 274nm as per the monograph given in the BP. According to BP specification, each tablet must contain 100±5% of the labeled amount of MT(BritishPharmacopoeia, 1998).The results are expressed in table 3.

Dissolution studies

a) *Single Point Dissolution Test:* The Dissolution test was performed using the USP<711> apparatus type I

(Erweka DT 600HH, Germany). The procedure specified in the USP was followed. Absorbance was measured using UV spectrophotometer (Model number WSB/4, Sr. no. 234A, Hamilton Lab Glass Ltd, UK) and percent drug released calculated. According to the USP, not less than 75% of the labeled amount of MT is dissolved in 30 minutes (USP28-NF23, 2004b). The results are shown in table 3.

b) *Dissolution Profile Comparison:* Dissolution profile of each marketed product was generated as per FDA (2000) guidelines in 0.1 N HCl (fig. 1) and phosphate buffers of pH 4.5 (fig. 2) and pH 6.8 (fig. 3). Dissolution profiles were studied and compared using model dependent and independent approaches.

a. Model independent approach: As a model independent approach, similarity factor (f_2) was determined by comparing the dissolution profiles of test (F1-F6 and brands B and C) and reference (brand A) products. Two dissolution profiles are considered similar when the f_2 value is between 50 and 100. When both test and reference products dissolve 85% or more of the label amount of the drug within 15 minutes using all three dissolution media proposed above, the profile comparison with an f_2 test is not recommended(FDA, 2000)

$$f_2 = 50 \times log[1 + {}^1\!/_n \left\{\sum (Rt - Tt)^2\right\}^{-0.5} \times 100]$$

Model dependent approach: In order to study the release kinetics of MT formulations, model dependent approach was adopted i.e. First Order, Weibull, Hixson-Crowell and Higuchi models were employed to analyze dissolution data obtained in simulated gastric fluid (0.1N HCl) using the software DDSolver. The goodness of fit of a model was assessed by the adjusted coefficients of determination ($r^2_{adjusted}$) and Akaike Information Criteria (AIC) (Zhang *et al*., 2010). Equations describing the various models are given below (Koester *et al*., 2004).

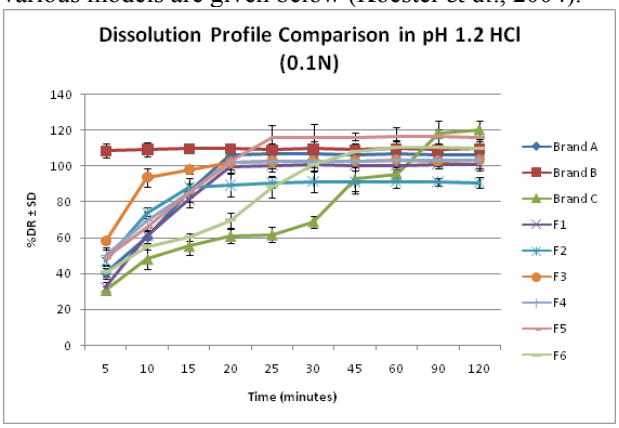

Fig. 1: Dissolution profile comparison in pH 1.2 HCl

Where Q_t is the amount of drug released in time t; Q_o the initial amount of drug in tablet; K_{HC}, K_1, k_H release rate constants; m is the accumulated fraction of drug; β the shape parameter; α the scale parameter; T_i the location parameter. The results are shown in table 4.

Model	Equation
First order	$\ln Q_t = \ln Q_o - K_1 t$
Hixson-Crowell	$Q_o^{\frac{1}{3}} - Q_t^{1/3} = K_{HC} \times t$
Higuchi	$Q_t = K_H t^{1/2}$
Weibull	$\log[-\ln(1-m)] = \beta \log(t - T_i) - \log a$

Stability studies

The trial formulations underwent accelerated stability testing as per ICH guidelines. The formulations were kept in amber colored glass bottles at 40±2°C temperature and 75±5% relative humidity for six months using a stability chamber (NuAire, USA). Disintegration time, friability, single point dissolution and content uniformity were evaluated at 1st, 3rd and 6th month (Allport-Settle, 2010). Results can be seen in table 5.

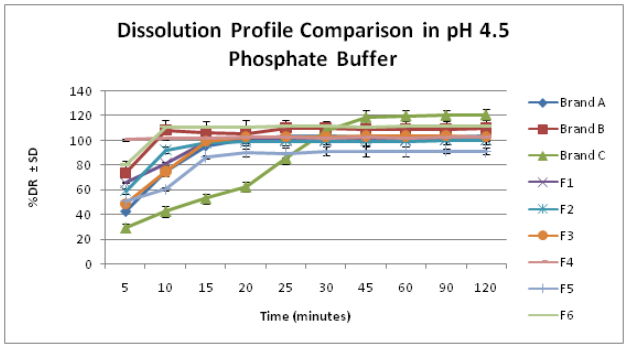

Fig. 2: Dissolution profile comparison in pH 4.5 Phosphate buffer.

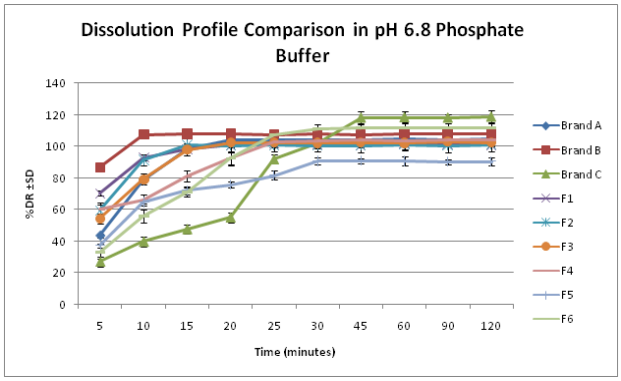

Fig. 3: Dissolution profile comparison in pH 6.8 Phosphate buffer.

RESULTS

Pre-formulation evaluation

In order to observe flow properties, the powder blends of trial batches (F1-F6) were subjected to the determination of angle of repose (θ) through fixed base method and Carr's index through their respective poured and tapped bulk densities (table 2). All powder blends were demonstrated as possessing good to excellent flow.

Table 1: Formulations 1-6

Ingredients	F1	F2	F3	F4	F5	F6
Metoprolol Tartrate	100mg	100mg	100mg	100 mg	100 mg	100
Avicel PH 102	40mg	80mg	100mg	120 mg	242 mg	662
Crospovidone	7mg	5mg	5mg	6 mg	7 mg	16
Magnesium Stearate	5mg	2mg	1mg	3 mg	1 mg	2
TOTAL WEIGHT	152mg	187mg	206mg	229 mg	350mg	780 mg

Table 2: Flow characteristics of powder blends

	Carr's Index (%)	Remarks	Angle of Repose (θ)
F1	14.481	Good	21.801
F2	12.702	Good	29.745
F3	14.732	Good	24.567
F4	9.381	Excellent	18.925
F5	9.401	Excellent	9.728
F6	8.222	Excellent	15.945

Table 3: Comparison of results

Code	Hardness (Kg)	Friability (%)	D*Time (min)	Thickness (mm)	Weight variation (mg)	DR** at 30 mins (%)	Content uniformity (%)
A***	13.947±2.903	0.199	19 minutes	4.115±0.074	343.87±3.830	106.75	104.153±4.890
B	4.055±0.747	0.333	5 minutes	4.168±0.068	348.99±13.234	109.56	109.319±0.332
C	14.608±2.077	0.091	11 minutes	4.739±0.092	273.54±3.115	68.99	120.946±0.332
F1	5.335±1.121	0.445	4 minutes	2.373±0.075	151.95±5.073	100.68±1.5	101.757±0.160
F2	8.270±1.099	0.076	13 minutes	3.056±0.163	187.94±7.914	91.52±5.98	103.088±1.027
F3	4.320±1.190	0.031	4 minutes	3.296±0.026	203.53±4.901	102.83±2.04	103.461±0.332
F4	8.298±1.339	0.374	17 minutes	3.724±0.118	229.47±3.007	103.65±3.43	102.716±3.467
F5	4.957±0.741	0.432	5 minutes	2.386±0.030	350.65±1.483	116.04±7.27	91.313±0.319
F6	4.344±0.474	0.291	5 minutes	2.326±0.031	779.40±2.311	101.22±4.27	111.224±0.332

* Disintegration, ** Drug Released, ***The brand is film coated

Table 4: Release kinetics of preparations

Model	Parameter	A	B	C	F1	F2	F3	F4	F5	F6
First order	$r^2_{adjusted}$	0.859	N/A	0.860	0.913	0.944	0.922	0.929	0.996	0.875
	K_1 (min^{-1})	0.121	N/A	0.050	0.108	0.127	0.208	0.138	0.011	0.078
	AIC	32.828	N/A	72.377	30.256	28.734	35.766	32.806	2.453	53.356
Hixson-Crowell	$r^2_{adjusted}$	0.931	N/A	0.858	0.967	0.937	0.979	0.940	0.868	0.881
	K_{HC} (min^{-1})	0.032	N/A	0.014	0.029	0.035	0.054	0.035	0.035	0.021
	AIC	29.268	N/A	62.532	19.576	19.219	14.836	19.978	31.817	44.740
Higuchi	$r^2_{adjusted}$	0.934	N/A	0.937	0.921	0.603	0.502	0.895	0.984	0.903
	K_H (min^{-1})	21.562	N/A	12.366	20.397	19.409	23.658	20.943	22.572	16.170
	AIC	29.008	N/A	64.311	29.813	40.516	34.658	35.211	21.309	51.352
Weibull	$r^2_{adjusted}$	0.916	N/A	0.861	0.989	0.984	0.982	0.954	0.766	0.900
	β	4.951	N/A	2.592	4.099	0.435	1.009	4.111	4.627	4.031
	AIC	30.762	N/A	73.747	20.621	25.103	18.450	31.250	35.187	52.861

Physical evaluation of tablets

Brands A and C and trial formulations F1 to F6 qualified the test of weight variation (table 3). With an average weight of 348.99±13.234mg, brand B alone failed this test as more than two tablets exceeded the limits (±5%) prescribed by the BP (British Pharmacopoeia, 1998).

All test products passed the test for thickness uniformity (table 3) except F2, with an average tablet thickness of 3.056±0.163mm.

All tablets were found to be adequately hard (table 3) to withstand shock and abrasion during transport and use, and percent weight loss after the friability test was within

Table 5: Accelerated stability testing of trial formulations 1 and 3

Study Period (month)	Test	F1	F3
0	Disintegration time (min)	4	4
	Friability (%)	0.445	0.031
	DR at 30 min (%)	100.68±1.5	102.83±2.04
	Content Uniformity (%)	101.757±0.160	103.461±0.332
1	Disintegration time (min)	4	4
	Friability (%)	0.445	0.031
	DR at 30 min (%)	100.93±0.5	103.08±1.75
	Content Uniformity (%)	101.002±2.994	103.850±2.515
3	Disintegration time (min)	4	4
	Friability (%)	0.446	0.031
	DR at 30 min (%)	101.47±2.1	104.52±3.01
	Content Uniformity (%)	102.018±1.764	103.426±1.639
6	Disintegration time (min)	5	6
	Friability (%)	0.446	0.032
	DR at 30 min (%)	102.020±1.7	105.601±1.05
	Content Uniformity (%)	103.010±3.286	104.404±3.221

the limit of 1% for each brand and within 0.8% for the trial formulations (table 3). The disintegration time of all market available brands and trial formulations F1, F2, F4-F6 was (table 3) was found to be within limits set by the USP i.e. less than 15 minutes for uncoated and less than 30 minutes for film coated tablets (USP28-NF23, 2004b). However, F3 failed the disintegration test as it took 19 minutes to disintegrate.

Brands A and Band the trial formulations F1-6, qualified the test for single point dissolution. Brand C alone failed to meet the United States Pharmacopoeial standard of dissolution i.e. not less than 75% in 30 minutes with a percent drug release of 68.99±3.1% at 30 minutes (see table 3) (USP28-NF23, 2004b).

Brand A and formulations 1 to 4 met the limits of BP (100±5%) for content uniformity of MT IR tablets (BritishPharmacopoeia, 1998). Whereas, brands B, C and F5, F6 failed to meet the specifications (table 3).

Dissolution studies

The dissolution profile of marketed brands and trial formulations were studied through model dependent and independent approaches.

Model independent approach

The drug release profile of innovator's product, brand A, was determined in different dissolution media i.e. pH 1.2 (0.1N) hydrochloric acid, phosphate buffer of pH 4.5 and pH 6.8 and maximum drug release was found at 30 minutes (106.75%) in pH 1.2 medium, 30 minutes (103.85%) in pH 4.5 medium and 60 minutes (104.96%) in pH 6.8 medium. Brand B, F2 and F3 (see figs. 1, 2 and 3) showed rapid drug release in each dissolution medium and were similar to the innovator product. When drug release profile of F1 in pH 1.2 dissolution medium was compared with brand A, the similarity factor (f_2) was calculated to be 59.842. The similarity factor for brand C was calculated in each medium. By virtue of results of f_2 analysis, it was found that brand C was not comparable to brand A (f_2=28.480 in pH 1.2; 30.413 in pH 4.5 and; 27.878 in pH 6.8). Furthermore, the value of f_2 when calculated for the profiles of F6 in dissolution media pH 1.2 and pH 6.8 was found to be 39.908 and 43.992, respectively. The similarity factor was also computed for F4 (f_2=51.300) and F5 (f_2=37.308) in dissolution medium of pH 6.8.

Model dependent approaches

For dissolution kinetic modeling, profiles obtained in pH 1.2 dissolution medium were analyzed for each formulation. As can be seen from table 4, the dissolution data of brand B could not be calculated perhaps because maximum drug release was attained almost immediately.

Akaike Information Criteria (AIC) and adjusted coefficient of determination ($r^2_{adjusted}$) of the test and reference formulations were compared. Lowest AIC and closer to 1 value of $r^2_{adjusted}$were the criteria used to determine the model that best fits the data (Zhang *et al*., 2010). The highest values of $r^2_{adjusted}$, i.e 0.931 for brand A, 0.0.858 for brand C, 0.967 for F1, 0.937 for F2, 0.979 for F3, 0.940 for F4, 0.868 for F5 and 0.881 for F6, were achieved using the Hixson-Crowell model. Furthermore, lowest AIC values were also obtained with this model, sequentially; 29.268, 62.532, 9.576, 19.219, 14.836, 19.978, 31.817 and 44.740. Therefore, the drug release was found to best fit the Hixson-Crowell model i.e., a the undergo a time dependent change in surface area and diameter (Singhvi and Singh, 2011). Moreover, Weibull shape parameter β values are more than 1 for reference and all test products except F2 indicating that these products have a release mechanism with an S-shaped curvature, followed by a turning point. F2 displayed $\beta < 1$, indicative of a parabolic curve with a steeper initial slope.

Stability studies

Accelerated stability testing was conducted only on trial formulations 1 and 3 (table 5) as of the six test formulations prepared, only F1 and F3 met all quality criteria applied.

F1 and F3 were determined to be stable under accelerated stress conditions as only minor changes in quality parameters were observed. Similar tests have been conducted by Sekar and Chellan (Sekar and Chellan, 2008) and Oliveira *et al.*(Oliveira *et al*., 2013). in order to ascertain stability of tablet formulations under stress conditions.

DISCUSSION

Preformulation characteristics of the powder blend were ascertained using well established indices, namely Carr's Index and Hausner's ratio (Alam *et al*., 2013, Kumar *et al*., 2011). The powder blend was found to possess good to excellent flow properties.

Physicochemical evaluation of tablets was performed using *in vitro* techniques that been employed by numerous other researchers (Raju *et al*., 2011, Satpute and Tour, 2013, Zafar, 2012). Most of the formulations, with the notable exception of brand B and brand C, met requirements.

Drug release from dosage forms involves multiple steps, rendering it difficult to obtain a mathematical model defining it correctly. When drug release is a result of an uncomplicated phenomenon or when that event is the rate limiting step, then it is easier to find a model to fit the drug release data. The Higuchi model is very appropriate for describing drug release from polymeric matrix systems(Costa and Sousa Lobo, 2001) while the Hixson-Crowell cube root law describes drug release from systems where a change in surface area and diameter of particles or tablets is seen. (Costa and Sousa Lobo, 2001, Singhvi and Singh, 2011). Generally, for tablets, the interaction of the processes of disintegration and dissolution is intricate and calls for models such as Weibull distribution (Yuksel *et al*., 2000). First order kinetic model was first applied by Gibaldi and Feldman to describe drug release rate that is concentration dependent(Kalam *et al*., 2007). Hence, dissolution profile comparison was performed using both model dependent and independent approaches. Yuskel *et al* in 2000 (Yuksel *et al*., 2000) and Shah *et al* in 1998 (Shah *et al*., 1998) are among researchers that have extensively studied the use of model independent approach to compare dissolution profiles. Polli *et al* investigated the wide dissolution specifications of Metoprolol in 1997 (Polli *et al*., 1997). Dressman *et al* (1998) studied the use of *in vitro* dissolution test as a predictive tool for peroral drug absorption from immediate release formulations (Dressman *et al*., 1998).

The use of DDSolver in studying dissolution kinetics has been well researched (Zhang *et al*., 2010). Many models other than the ones used in present study have been employed by pharmaceutical researchers to elucidate drug release kinetics (Hurtado y de la Pena *et al*., 2003, Zhang *et al*., 2010, Zuo *et al*., 2014).

Many research scientists have used the methods described to elucidate kinetics of drug release from immediate release tablet formulations (Medina *et al*., 2014, Rath *et al*., 2011). Hixson-Crowell model best fit dissolution data and F1 most closely followed the reference product among the trail formulations.

Finally, stability testing was done as it describes numerous factors that can influence the expiry date of a dosage form, such as physicochemical stability during formulation development, packaging and post-marketing stages. Lack of stability may affect purity, strength and safety of the product. Thus, stability testing aids in the establishment of manufacturing and storage conditions, shelf life and expiry date (Melveger and Huynh-Ba, 2009). F1 was found to have best withstood accelerated stability testing conditions.

CONCLUSION

Six immediate release trial formulations (F1-6) of Metoprolol Tartrate were manufactured by direct compression and their quality attributes were compared to those of commercially available products. The reference product (brand A) met all applicable standards of quality. The other (brands B and C) marketed products failed to satisfy all requirements. Only formulations 1 and 3 passed all physical and chemical tests. F2 did not meet the criterion of the thickness test, while the dissolution profile of F4 in medium of pH 6.8 was dissimilar to the reference brand, and formulations 5 and 6 did not pass content uniformity test. Based on $r^2_{adjusted}$ and AIC values, Hixson-Crowell model best fit the dissolution data. F1 was found to most closely resemble and A and may be declared the optimized formulation.

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