Research Article

www.ijrap.net

(ISSN Online:2229–3566, ISSN Print:2277–4343)

FORMULATION AND EVALUATION OF ENTERIC-COATED TABLETS OF BISACODYL

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Received on: 12/12/21 Accepted on: 10/01/22

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DOI: 10.7897/2277-4343.13019

ABSTRACT

The present study aims to design and formulate the enteric-coated tablets of bisacodyl and comply with the physicochemical properties per BP limits. The wet granulation technique prepared the formulations. As a result of the studies, the blend of all formulations showed good flow properties such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The prepared tablets were indicated suitable post-compression parameters like Hardness, Thickness, weight variation, friability, content uniformity, disintegration time, In vitro dissolution studies. In the FTIR studies, all the excipients were tested for compatibility with the drug, revealing that no physical and chemical interaction occurred. The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of 0.1N HCL at 100 rpm at a temperature of 37±0.5 ˚C. The formulation F7 consisting of Solutab was best among all the formulations; it has exhibited a faster disintegrating time (2 min and 17 sec.) compared to other formulations.

Keywords: Bisacodyl tablets, FTIR, wet granulation technique, compatibility.

INTRODUCTION

Drugs are rarely administered as pure chemical substances alone and are almost always formulated preparations or medicines. The development of dosage forms draws on the discipline of biopharmaceutics, which integrates an understanding of formulations, dissolution, stability, and controlled release (pharmaceutics); absorption, distribution, metabolism, and excretion (pharmacokinetics, PK); concentration-effect relationships and drug-receptor interactions (pharmacodynamics, PD); and treatment of the disease state (therapeutics). A drug is a substance used to cure, treat, restore health, or optimize a malfunction. Formulation of a dosage form typically involves combining an active ingredient and one or more excipients; the resultant dosage form determines the route of administration and the clinical efficacy and safety of the drug. Optimization of drug doses is also critical to achieving clinical efficacy and safety[1].

Oral dosage forms are the most frequently used route of administration among all routes. Oral drug delivery is the most widely utilized route of administration among all the ways that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form[2]. The oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. The oral route of drug administration has wide acceptance up to 50 to 60% of total dosage forms. Due to its advantages, solid dosage forms are the famous and most preferred route. The most popular dosage forms are being tablets[3]. Tablet is a pharmaceutical solid dosage form comprising a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The tablets dosage form is one of the most preferred dosage forms all over the world[4]. In other words, pharmaceutical tablets are solid flat or biconvex disc's prepared by compressing a drug or a mixture of drugs, with or without diluents[5].

Traditionally, granulation has made tablets, which imparts two primary requisites to formulate: compatibility and fluidity[4]. Both wet and dry granulation (slugging and roll compaction) are used. Numerous unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulation, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability[6]. Tablet coating is a common pharmaceutical technique of applying a thin polymer-based film to a tablet or a granule containing active pharmaceutical ingredients (APIs)[5]. Coated tablets are defined as tablets covered with one or more layers of a mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol, waxes, authorized colouring material and sometimes flavoring material. The coating may also contain active ingredient[6]. Substances used for coating are usually applied as solution or suspension under conditions where the vehicle evaporates[7]. The word "enteric" indicates the small intestine; therefore, enteric coatings prevent the release of medication before it reaches the small intestine. The enteric-coated polymers remain to unionise at low pH and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups can ionise, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers[7].

The present study aims to design and formulate the enteric-coated tablets of bisacodyl and comply with the physicochemical properties per BP limits. Bisacodyl is highly acid liable, and it is used as a stimulant laxative drug that works directly on the colon

to produce a bowel movement. It is typically prescribed to relieve constipation and manage neurogenic bowel dysfunction and part of bowel preparation before medical examinations. To achieve these goals, various prototype formulation trails were taken by wet granulation method using different diluents and observing differences in the in-process parameters such as dissolution, assay for complying with the data as per BP limits under quality control.

MATERIALS AND METHODS

Bisacodyl was gifted from JPN Pharma Pvt. Ltd., India. Dibasic calcium phosphate was obtained from Rhodia. Lactose anhydrous was obtained from Loba chem, India. Povidone was obtained from Blagden speciality chemicals. Aerosil was received from Wacker chemical corporation. Isopropyl alcohol was obtained from Ranchem, India. HPMC 15 cps was obtained from Dow chemicals. Eudragit L- 100 was procured from Evonik industries.

Manufacturing procedure

Accurately weighed Bisacodyl, Kaolin, Dibasic calcium phosphate, Starch, Croscarmellose sodium and Lactose anhydrous, weighed materials were co-sifted together by geometric dilution method through #30 and #60 meshes and placed in a separate polythene bag. They are used as a dry mix. Accurately weighed, povidone is added to isopropyl alcohol and stirred well to get a clear solution, and this clear solution is used as a binder solution. The sifted materials were mixed for 5 mins in a polythene bag before granulating and transferred to a vessel and granulated with the required quantity of binder solution by kneading method (hand granulation). The granules were dried in a hot air oven at 40-500 C. Then semi-dried granules were passed through sieve No. 20 and continued drying till the moisture content of granules was less than 1.0 %. Then after obtaining the optimum moisture content, granules were removed from the oven. The dried granules were sifted through the #30 mesh to achieve uniform particle size. The above granules were mixed with croscarmellose sodium and mixed well. They were finally lubricated with the required quantity of colloidal silicon dioxide and magnesium stearate after sifting it through #60 mesh for 2 mins. The lubricated granules were then compressed into tablets with an average weight of 120 mg initially using 8.00 mm punches7. The formulation chart for preparation of bisacodyl enteric-coated tablet showed in Table 1.

Table 1: Formulation chart

Ingredients (mg)	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Bisacodyl	5.1	5.1	5.1	5.1	5.1	5.1	5.1
Dibasic calciumphosphate	0	10	15	19	19	19	19
Kaolin	13	18	15	25	18	18	4
Starch	32	30	26	0	20	20	24
Lactose anhydrous	40	40	27	20	0	27	37
Microcrystallinecellulose	0	0	0	20	27	0	0
Croscarmellosesodium	3	3	2	2	2	2	2
Lactose anhydrous	13	0	0	0	0	0	0
Sodium laurylsulphate	0	0	1	0	0	0.3	0.5
Povidone K-30	3	3	3	4	4	4	3
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Starch	5	6	4	2	2	2	2
Croscarmellosesodium	6	5	2	3	3	3	3
Colloidal silicondioxide	0.2	0.2	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	0.2	0.2	0.25	0.25	0.25	0.25	0.25
Average weight	120mg	120mg	100mg	100mg	100mg	100mg	100mg

Table 2: Composition of Ingredients for Seal Coating

Ingredients	Quantity (gm)
HPMC 15 cps	2.4
Talc	0.6
Titanium dioxide	0.6
Propylene glycol	0.4
Purified water	Q.S

Table 3: Composition of Ingredients for Enteric Coating

Ingredients	Quantity (gm)
Poly methacrylic acid -methyl acrylate (1:1)	7.854
Talc	2.142
Titanium dioxide	1.856
Triethyl citrate	1.856
Quinoline yellow lake	0.572
Purified water	Q.S

Table 4: Operation condition for Seal and Enteric Coating Process

Specifications	Range	
	Seal coating	Enteric coating
Pan diameter	12”	12”
Speed of pan revolution	8-10 rpm	10-12 rpm
Distance of spray gun	5-6”	5-6”
Spray nozzle diameter	1.2 mm	1.2 mm
Spray rate	2.5-3 ml /min	1.5 -2.0 ml /min
Dry air temperature	50 ± 5/ 30 mins	50 ± 5^0C / 30 mins
Coating time	2 hours	4 hours
Bed temperature	30-40^{0}C	30-40^{0}C

Table 5: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of repose
Excellent	25-30
Good	31-35
Fair aid is not need	36-40
Passable may hang up	41-45
Poor must agitate vibrate	46-55
Very poor	56-65
Very very poor	>66

Table 6: Scale of Flowability

Compressibility Index (%)	Flow character	Hauser ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Table 7: The chromatographic conditions were set as per BP specifications

Apparatus	HPLC
Column	A stainless-steel column (25cm x 4.6mm) packed with base-deactivated octadecylsilyl silica gel (5µm) usuallywater's symmetry (C_{18}) is suitable.
Wavelength	265nm
Flow rate	1.5ml/min
Column temperature	Ambient
Detector	Photodiode array
Inject volume	50µL

Table 8: Storage conditions for various stability studies

Study	Storage Condition
Long term	25°C±2°C / 60%RH±5%RH
Intermediate	30°C±2°C / 65%RH±5%RH
Accelerated	40°C±2°C / 75%RH±5%RH

Table 9: Pre Compression parameters for powder blend

CODE	Bulk density *(g/ml)	Tapped density *(g/ml)	Compressibility Index *(%)	Hausner's Ratio *	Moisture Content (%)
F1	0.376±0.007	0.430±0.005	12.49±0.007	1.14±0.002	1.58
F2	0.380±0.001	0.464±0.002	18.14±0.006	1.22±0.001	1.39
F3	0.382±0.001	0.449±0.004	14.99±0.009	1.17±0.006	1.54
F4	0.387±0.007	0.471±0.003	17.83±0.004	1.21±0.007	1.66
F5	0.386±0.002	0.461±0.002	15.70±0.002	1.17±0.007	1.22
F6	0.378±0.001	0.408±0.006	7.50±0.001	1.08±0.009	1.05
F7	0.374±0.005	0.394±0.002	4.99±0.007	1.05±0.007	0.92

*All the values are mean ±SD, n=3

Table 10: Sieve analysis for the powder blends of formulations

Sieve No.(#)	Sieve aperture (µm)	% Retained						
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
20	850	2.39	1.27	0.69	2.19	0.39	3.18	1.58
40	425	17.80	10.23	7.70	12.98	8.71	21.11	8.98
60	250	43.15	20.51	26.46	39.95	24.18	40.83	23.75
100	150	77.68	65.61	58.20	76.90	51.07	83.86	55.88
Pan	…	96.00	99.28	98.72	99.36	98.64	99.60	99.50

Table 11: Evaluation of post-compression parameters for core tablets

CODE	General appearance	Weight variation (mg)	Thickness* (mm)	Friability* (%)	Hardness* (kg/cm^2)	DisintegrationTime # (minutes)
F1	Round,Convex	120±0.5	2.87±0.01	0.28±0.09	7.0±0.2	7min 45sec ±0.011
F2	Round, Convex	120±0.5	2.95±0.02	0.35±0.02	6.5±0.1	8min10sec ±0.056
F3	Round, Convex	100±0.6	3.02±0.10	1.32±0.03	6.0±0.2	7min 15sec ±0.018
F4	Round, Convex	100±0.3	3.00± 0.08	0.19±0.04	5.3±0.3	6min 10sec ±0.052
F5	Round, Convex	100±0.2	3.09±0.03	0.24±0.05	6.5±0.3	9min 50sec ±0.031
F6	Round, Convex	100±0.9	3.10±0.04	0.15±0.02	4.0±0.8	5min 10sec ±0.045
F7	Round, Convex	100±0.1	3.20±0.05	0.10±0.01	3.0±0.2	2min 17sec ±0.021

*All the values are mean ±SD, n=3#All the values are mean ±SD, n=6

Table 12: Evaluation of post-compression parameters for enteric coated tablets

Code	AverageWeight* (mg)	Thickness (mm)*	Hardness*(Kg/cm^2)	DisintegrationTime # (minutes)	Assay (%)*
F7	109.15±0.04	3.14±0.03	4.0±0.1	6min23sec ± 0.02	99.92 ±0.08

*All the values are mean ±SD, n=3#All the values are mean ±SD, n=6

Table 13: *Invitro* dissolution profile for the innovator product andformulation (F7)

Dissolution medium	Sampling time	% Drug release	
Simulated gastric fluid (0.1NHCL)	120 minutes	**Innovator**	**F7**
		0.276%	0.055%
Simulated intestinal fluid(pH 7.4 phosphate buffer)	45 minutes	87.37%	90.74%

Table 14: *Invitro* dissolution profile comparison using similarity factor for theinnovator product with the sample (F7)

Time(min)	Reference (R)	Test (T)	$R_T - T_T$	$(R_T - T_T)^2$	$\|R_T - T_T\|$
0	0.00	0.00	0.00	0.00	0.00
15	31.37	33.55	- 2.18	4.752	2.18
30	63.73	67.03	-3.3	10.890	3.3
45	87.37	90.74	-3.37	11.356	3.37

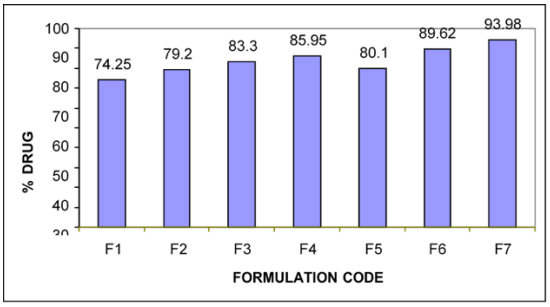

Figure 1: *In-vitro* Dissolution profile of core tablets for various formulations (F1- F7)

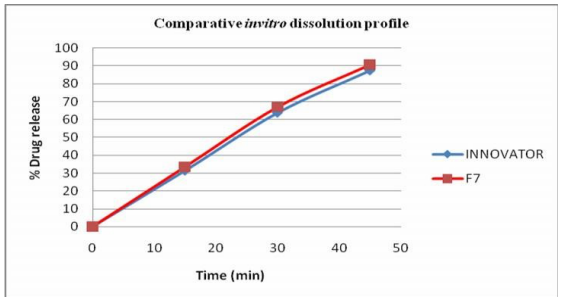

Figure 2: Comparative *Invitro* dissolution profile for the innovator with formulation (F7)

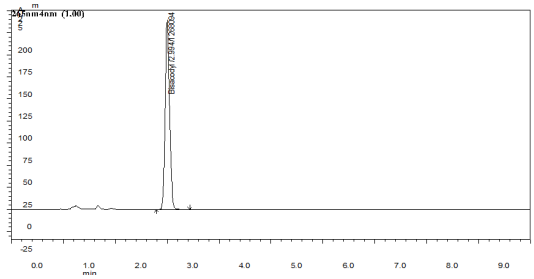

Figure 3: Standard chromatogram of Bisacodyl

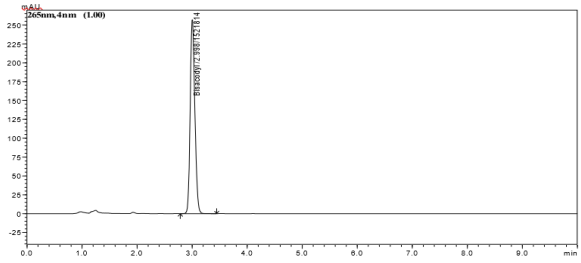

Figure 4: Sample chromatogram

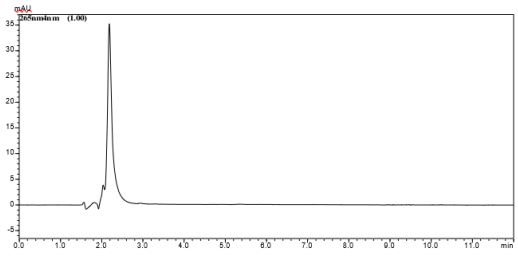

Figure 5: Blank chromatogram

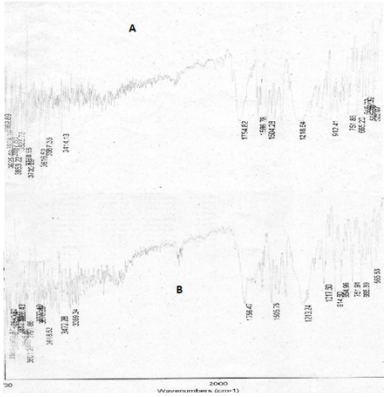

Figure 6: FTIR spectra of A. Pure drug and B. optimized formulation

Table 15: Accelerated stability data of physical parameters for the formulation (F7)

Physical parameters	Storage conditions			
	40˚C±2˚C / 75% RH±5% RH			
	Initial	1st month	2nd month	3rd month
Description	Pale yellow, roundenteric coated tablet	Pale yellow, round enteric coated tablet	Pale yellow, round enteric coated tablet	Pale yellow, round enteric coated tablet
Average weight*(mg)	109.15±0.04	109.21±0.02	109.55±0.04	109.89±0.01
Hardness*(kg/cm^2)	4.0±0.1	3.8±0.2	4.2±0.1	3.5±0.15
Thickness*(mm)	3.14±0.03	3.14±0.08	3.15±0.01	3.14±0.05
Disintegrationtime	6min23sec ± 0.02	6min 40sec ± 0.02	7min 10sec ± 0.05	6min 89sec ± 0.07

*All the values are mean ±SD, n=3

Table 16: Accelerated stability data of Invitro dissolution and assay for the F7

Parameters	Specifications	Storage conditions			
		40˚C±2˚C / 75% RH±5% RH			
		Initial	1st month	2nd month	3rd month
Simulated gastric fluid(0.1N HCL)	NMT 5% in 120 minutes	0.055%	0.063%	0.087%	0.109%
Simulated intestinal fluid(pH 7.4 phosphate buffer)	NLT 75% in 45 minutes	90.74%	89.95%	89.18%	88.69%
Assay (%)	95.0 to 105.0%	99.92%	99.54%	98.61%	89.87%

Coating Formula

Seal coating: Seal coating is important for preventing direct interaction between bisacodyl and polymer. Seal coating is performed for the core tablet of formulation (F7). When 2% build-up is given, the weight of the seal coated tablet was found to be 102mg per tablet. The composition of ingredients for seal coating was tabulated in Table 2.

Preparation of seal coating solution: Weighed a required quantity of HPMC 15 cps accurately soaked in water for 30 min and stirred until it swelled. Meanwhile, talc and titanium dioxide were triturated in a mortar, added to the above solution and stirred. Followed by propylene glycol as a plasticizer is added furtherly and stirred**.** Filter the above solution in the #100 mesh. Finally, the volume was made up to the required quantity with purified water.

Enteric Coating: Enteric coating is performed to protect the drug from an acidic environment. The seal coated tablets were subjected to enteric coating, where the weight of the enteric-coated tablets was found to be 109.14mg when 7% build-up was given[7]. The composition of ingredients for enteric coating was tabulated in Table 3.

Preparation of Enteric Coating solution

A required quantity of Methacrylic acid copolymer powder was weighed accurately and kept stirring with the required amount of water. Meanwhile, talc, titanium dioxide and quinoline yellow lake were triturated separately in a mortar until making a paste by adding the water and added to the above solution and stirred. Filter the above solution with #100 mesh. Finally, the volume was made up to the required quantity with purified water[7]. Operation condition for Seal and Enteric Coating Process was shown in Table 4.

Drug-Excipient Compatibility Study by Fourier Transform Infrared Spectroscopy (FTIR)[8]

The FT-IR spectra of pure Telmisartan and prepared optimized formulation of chitosan loaded nanoparticles were recorded using FTIR (Bruker Alpha-T, Switzerland) to investigate any interaction between telmisartan and polymers in formulated nanoparticles. The samples were ground with KBr and pressed into a disk shape for measurement. The prepared pellets were scanned over a frequency range of 4000-400 cm^{-1}.

Evaluation of pre-compression parameter for powder blend[8-10]

Angle of repose: The angle of repose of API powder is determined by the funnel method. The accurate weight powder blend is taken in the funnel. The height of the funnel is adjusted so that the tip of the funnel just touched the apex of the powder blend. The powder blend can flow through the funnel freely on the surface. The diameter of the powder cone is measured, and the angle of repose is calculated using the following equation. Flow properties and corresponding angle of repose values are shown in Table 5.

$$\tan \theta = h/r$$

where h and r are the height and radius of the powder cone.

Bulk density: The powder sample under test is screened through sieve No.18, and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is levelled, and the unsettled volume, V_o is noted. The bulk density is calculated in g/cm^3 by the formula.

$$\text{Bulk density} = M/V_0$$

M= Powder mass, V_0= apparent unstirred volume

Tapped density: The powder sample under test is screened through sieve No.18, and the weight of the sample is equivalent to 25 gm filled in a 100 ml granulated cylinder. The mechanical tapping of the cylinder is carried out using tapped density tester at a nominal rate 500 times initially, and the tapped volume V_0 is noted. Tappings are preceded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volumes is less than 2%, and Vb is considered a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.

$$\text{Tapped density} = M/V_f$$

M= weight of sample power taken, V_f= tapped volume

Compressibility Index: The Compressibility Index of the power blend is determined by Carr's compressibility index to know the flow characteristics. The formula for Carr's Index is shown

below. The flowing character for powders is displayed in Table 6.

$$\text{Carr's Index (\%)} = [(TD-BD)/TD] \times 100$$

Hauser's ratio: Hauser's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is Hauser's ratio.

$$H=\rho T / \rho B$$

Where ρT= tapped density, ρB = bulk density

Post compression parameters[11]

Thickness: The thickness of tablets was determined by using a digital micrometre. Ten individual tablets from each batch were used, and the results averaged.

Hardness test: Tablets require a certain amount of strength or hardness to withstand mechanical handling shocks in manufacture, packaging and shipping. Hardness can be defined as the strength of the tablet to withstand the pressure applied. In this test, a pill was laced between two anvils, the force was applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hence hardness is sometimes referred to as "Crushing Strength".

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of the three batches were calculated. It passes the test weight variation test if not more than two of the individual tablet's weights deviate from the average weight by more than the allowed percentage deviation and more deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Friability: The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed, six tablets were placed in Roche friabilitor and rotated at 25rpm for 4 min. Percentage friability was calculated using the following equation.

$$\text{Friability} = ([\ w_0\text{-}w] / w_0) \times 100$$

Assay: The content of the drug was carried out by five randomly selected tablets of each formulation. The five tablets were ground in a mortar to get powder. This powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 254 nm using a UV spectrophotometer. Each measurement was carried out in triplicate, and the average drug content was calculated.

Disintegration test: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. The apparatus was run for 10 minutes, and the basket was lifted from the fluid to observe whether all of the tablets had disintegrated.

Dissolution test of prepared tablets[12]
Dissolution at Acid stage medium
Apparatus: Type II paddle
Speed: 100 rpm
Duration: 2 hours
Time points: Up to 2 hours
Temperature: 37˚C ± 0.5˚C
Medium: 500ml of 0.1N HCL
Sample withdrawn: 10 ml

Dissolution media Preparation

Preparation of 0.1N HCL: 8.5 ml of concentrated HCL was added to 1000 ml of purifiedwater, and the pH was adjusted to 1.2.

Standard Preparation: Accurately weighed and transferred 10.0 mg of bisacodyl in 100 ml standard flask, added 5 to 10 ml 0.1N HCL to dissolve the drug entirely, and volume was made up with the same medium up to 100ml. From this primary stock solution, pipette out 10 ml and transferred to 100 ml standard flask and made up the volume with 0.1N HCL (pH 1.2) medium.

Dissolution procedure: Apparatus was set as per the above conditions. One tablet was placedin each of the six-dissolution bowls containing 500ml of 0.1N HCL as a medium. The dissolution test was performed for 2 hours. An Aliquots of the dissolution medium was withdrawn at the specified time and filtered.

Sample injection procedure: 50 µl of sample preparation and standard preparation were injected into the liquid chromatography and recorded the chromatogram. The major peaks were recorded and calculated for the assay quantity of bisacodyl in percentage from the peak areas of standardand sample preparation. The mentioned formula calculated the percentage of bisacodyl drug released at the end of 2 hours.

BP limits: NMT 5% of the stated amount of bisacodyl is dissolved in 2 hours.

Dissolution at Buffer stage medium:
1. **Apparatus:** Type II paddle
2. **Speed:** 100 rpm
3. **Duration:** 45minutes
4. **Time points:** 15, 30, 45 minutes
5. **Temperature:** $37^0C \pm 0.5^0C$
6. **Medium:** 900ml of phosphate buffer pH 7.4
7. **Sample withdrawn:** 10ml

Dissolution media Preparation[12]

Preparation of phosphate buffer (pH 7.4): 7.80 g of sodium dihydrogen orthophosphate in sufficient water to produce 1000 ml. Add 5.0 g of sodium dodecyl sulfate, heat to dissolve and adjust the pH to 7.4.
Standard Preparation: Accurately weighed and transferred 56.0 mg of bisacodyl in 100 ml standard flask, added 5 to 10 ml acetonitrile to dissolve the drug altogether, and volume was made up with the same medium up to 100ml. This primary stock solution pipetted out 10 ml, transferred to 100 ml standard flask, and made up the volume with pH 7.4 buffer medium.
Dissolution procedure: Apparatus was set as per the above conditions; one tablet was placed in each of the six-dissolution bowls containing 900 ml of pH 7.4 as buffer medium. The dissolution test was performed for 45 minutes. An Aliquots (10 ml) of the dissolution medium was withdrawn at the specified time points from each bowl and filtered through 5 µm filter paper.
Sample injection Procedure: 50 µl of sample preparation and standard preparation were injected into the liquid chromatography and recorded the chromatogram. The major peaks were recorded and calculated for the assay quantity of bisacodyl in percentage from the peak areas of standard and sample preparation, and the percentage of bisacodyl drug released at the end of 45 minutes was calculated by the mentioned formula

$$\% \text{ release} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{100} \times \frac{900}{5} \times \frac{98.15}{100} \times 100$$

where, AT= Sample area AS = Standard area and WS = Working standard

BP limits: NLT 75% of the stated amount of bisacodyl is dissolved in 45 mins.

Assay by HPLC method[13]

Chromatographic conditions: The chromatographic conditions were set as per BP specifications shown in Table 7.
Preparation of mobile phase: A mixture of 45 volumes of acetonitrile and 55 volumes of 0.025M ammonium format was previously adjusted to pH 5.0 with anhydrous formic acid.
Preparation of diluent: A mixture of 4 volumes of glacial acetic acid, 30 volumes of acetonitrile and 66 volumes of distilled water was prepared as a diluent for assay.
Preparation of phosphate buffer (pH 7.4): 7.80g of sodium dihydrogen orthrophosphate in sufficient water to produce 1000 ml. Add 5.0 g of sodium dodecyl sulfate, heat to dissolve and adjust the pH to 7.4.
Preparation of standard solution: 50mg of bisacodyl RS was accurately weighed and transferred into a 100 ml clean, dry volumetric flask and dissolved in a bit of quantity of acetonitrile, sonicate for 5 minutes and make up the volume. From this stock solution, 5 ml was transferred into a 50 ml volumetricflask and made up the volume with buffer medium.
Preparation of sample solution: For the estimation in dosage form, 20 tablets were weighed and powdered. An amount equivalent to 10 mg of bisacodyl from powdered tablets was accurately weighed and transferred to a 200 ml volumetric flask; add about 10 ml of acetonitrile mixture and sonicate for 15 minutes. Cool the solution to room temperature and make up the volume with the same diluent. Filter a portion of the above solution and pipette out 5 ml of the filtrate, transfer to 50 ml volumetric flask, and make up the volume with buffer.
Sample injection procedure: 20 µl of a filtered portion of the standard preparation (five injections) and sample preparation were separately injected into the chromatographic system. The chromatograms were recorded, and the responses were measured for the major peaks. The content of bisacodyl present in each tablet was calculated using the following expression.

$$\% \text{ content} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{50} \times \frac{50}{\text{spl. wt.}} \times \frac{P}{100} \times \text{Avg. wt.} \times 100$$

where, AS = Standard area, AT = Sample area, WS = Standard weight, Spl Wt = Sample weight, Avg.Wt = Sample average weight

Comparative *Invitro* dissolution profile study: In recent years, the FDA has emphasised a dissolution profile comparison in post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes or different strengths helps assure similarity in product performance and signals bio in equivalence. Comparing therapeutic versions of two medicinal products containing the same active substance is critical for assessing the possibility of alternative uses between the innovator and any similar medicinal product. Dissolution profiles of two products can be considered identical under -

Overall profile similarity, and
Similarity at every dissolution sample time point.

A simple model-independent approach uses a difference factor (f_1) and a similarity factor(f_2) to compare the dissolution profiles. The difference factor calculates the percentage difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

Where n is the number of time points, R_t is the dissolution value of the reference batch attime t, and T_t is the dissolution value of the test batch at time t.

The similarity factor f_2 is a logarithmic reciprocal square root transformation of the squared error sum and is a measurement of the similarity in the percent dissolution between thetwo curves.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

General procedure:
1. Determine the dissolution profile of two products (6 units each) of the test andreference products.
2. Using the mean dissolution values from both the curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.
3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be 100. Generally, f_1 values up to 15 (0-15) and f_2 values greaterthan 50 (50-100) ensure the sameness or equivalence of the two curves.

The comparative dissolution study was performed to determine the similarity of dissolution profiles for bisacodyl enteric-coated tablets between the innovator product with the optimized formulation. **(F7).**

Stability studies[12]: The stability of a drug has been defined as the ability of a particular formulation in a specific container to remain within its physical, chemical, therapeutics and toxicological specifications throughout its shelf life.

Stability testing provides evidence as to how the quality of the drug product varies with time. Establish shelf life for the drug product. Determine recommended storage conditions. Determine container closure system suitability.

Accelerated stability studies: Generally, observing the rate at which the product degrades under normal room temperature requires a long time. The International Conference of Harmonization (ICH) Guidelines titled "Stability testing for new drug substances and product" (Q1A) describes the stability test requirements for drug registration application in the European Union and the United States of America. The accelerated stability was carryout by ICH guidelines. The ICH guideline recommends the following storage conditions for stability studies depicted in Table 8.

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75% RH±5% RH for three months. As per the standard protocol, the samples must be analysed at 0, 1, 2, and 3 months' time points. Accelerated stability studies were performed for the final enteric-coated tablets. The tablets were packed in blister packing material and loaded into the stability chamber under 40±2˚C / 75% ±5% RH, and the samples were analyzed at 0, 1, 2 and 3 months' time points.

Test Performed

1. Test for physical parameters (description, hardness, thickness, friability, disintegration).
2. Assay.
3. *In-vitro* Dissolution Study.

RESULTS AND DISCUSSION

Evaluation of pre-compression parameters for powder blend: The pre-compression parameters for the powder blend or granules were evaluated per the procedure mentioned in the methodology part, and the results were tabulated in Table 9.

The flow properties of prepared granules of various formulations of bisacodylwere given in Table 10. Flow properties of the resistance of the granules to particlemovement can be judged from the bulk density, tapped density, compressibility index, Hausner's ratio. This measurement gives a qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabletting. The bulk density was found within 0.374 to 0.382 g/ml. Thetapped density was found within 0.394 to 0.471 g/ml; the Hausner's ratio and compressibility index were calculated using the density data. Hausner's ratio was found within 1.05 to 1.22, indicating better flowability. The Compressibility index was found within 4.99 to 18.14%, indicating good flow properties.

Evaluation of post-compression parameters for compressed tablets

The post-compression parameters were evaluated for the core and enteric-coated tablet. Their results were tabulated in Table 11 & *invitro* dissolution profile of core tablets for various formulations was depicted in Figure 1.

Limits

1. The amount of bisacodyl released in the case of simulated gastric fluid (0.1 N HCL) is Not More Than 5% of the stated amount.
2. The amount of bisacodyl released in case of simulated intestinal fluid (pH 7.4) is Not Less Than 75% (Q) of the stated amount.

Comparative *Invitro* dissolution study using similarity factor

On substituting the observed values in the appropriate formula, the difference factor (f_1) and the similarity factor (f_2) was found to be 5.32 and 75.08.

ASSAY: The HPLC method carried out the assay determination for the blank, standard, and sample. Standard chromatogram of bisacodyl: The peak area plot of the standard bisacodyl chromatogram is given in Figure 3.

Sample Chromatogram: The peak area plot of the sample chromatogram is given in Figure 4.

Blank chromatogram: The peak area plot of the bisacodyl blank chromatogram is given in Figure 5.

FTIR Compatibility studies: Characteristic absorption peaks of pure drug and a mixture of other excipients were obtained at different wave numbers. The characteristic peaks were observed aromatic -C-C stretching 1435.18 cm^{-1}, alkane rocking at -C-H 1370.27 cm^{-1} and C-N aromatic stretching 1267.28 cm^{-1}obtained in pure drug and optimized formulation. The above results indicated no incompatibility between the drug and excipients used and the FTIR graph shown in Figure 6.

STABILITY STUDIES

The formulation (F7) of enteric-coated tablets were carried out for the accelerated stability studies for three months at 40˚C±2˚C / 75% RH±5% RH in the stability chamber. The resulted data are given in Tables 15 and 16. The results reveal no significant changes in the physical parameters at the end of the 1st, 2nd, 3rd months. The drug content and in vitro dissolution profile remained without any significant changes at the end of the 1st, 2nd, 3rd months. Hence, it is concluded that the formulated enteric-coated tablets are stable, and the data obtained could be used to predict the product's shelf life.

DISCUSSION

The present aim of the work is to develop and formulate stable bisacodyl enteric-coated tablets and comply with the in vitro dissolution parameters with the innovator product. As per British pharmacopoeias specifications (BP 2013), the bisacodyl tablets shouldadhere to the in-vitro dissolution test prescribed in the monograph. As per specifications, the amount of bisacodyl released in the dissolution medium is not more than 5% in the acid medium and Not Less Than 75% (Q) of the stated amount in the case of pH 7.4 phosphatebuffer medium. Since bisacodyl is a highly acid liable drug, it is necessary to formulate the tablet as enteric-coated tablets, which resists the drug-releasing in the stomach.

In this work, the wet granulation method formulated all the core tablets by using povidone as a binder. Aqueous coating is performed for both seal and enteric coating processes. The present work was initiated with the preformulation studies for the API and evaluated parameters like description, solubility analysis, moisture content, micrometric properties and particle size determination. The evaluating in-process parameters for the powder blend are bulk density, tapped density, compressibility index, moisture content and Hausner's ratio. The compressed tablets were evaluated for thickness, hardness, friability, assay and in-vitro dissolution study. The impacts observed from the various in-process parameters for the powder blends and compressed tablets were discussed one by one below.

Pre formulation studies

Evaluation of Active Pharmaceutical Ingredient (API): The preformulation studies for the API reveal that the description of the bisacodyl powder was appeared as white crystalline and had no odour. Based on the solubility analysis, the API was insoluble in water whereas soluble in acetone and isopropyl alcohol. The moisture content was found to be 0.96% at 60^0C. The micrometric properties of API were satisfactory, and it shows a moderate flow property. The particle size determination was performed by the sieving method. It shows that almost 99.60% of the drug passes through all the sieves, and it is a moderately coarse powder. The drug-excipients compatibility study observed no significant change or interaction between drug and excipients on storage conditions at 40^0C / 75%RH for two weeks.

Evaluation parameters

Evaluation of Pre-Compression parameters for Powder Blend: The results of the evaluation of powder blends for all the formulations (F1 to F7) were given in Table 9; it suggests that it has good flow property. The bulk density values observed from the formulations F1 to F7 was found to be within the range of 0.374 to 0.387g/ml. The formulation F7 shows the lowest value when compared to other formulations. The tapped density values observed from the formulations F1 to F7 was found to be within range 0.374 to 0.464g/ml. Settling down granules for F1 to F5 is difficult when tapping, whereas F6 and F7 formulation is not difficult. The compressibility index for the formulations F1 to F5

was within the range of 12.49 to 18.14 %, which shows proper flow in granules. In contrast, formulations F6 and F7 show better flow characters than the other five. Hausner's ratio for F1 to F7 was found within 1.05 to 1.22. From the observed values, the flow type was good for all formulations.

Evaluation of Post Compression parameters for core tablets: The results of compressed core tablets are given in Table 11. All the formulation batches of core tablets show an excellent appearance. In the formulation F1, with the presence of diluents-kaolin (10.83%), lactose anhydrous (40.83%) were added in intra and extra granular part, starch (26.6%), and povidone (2.5%), it shows that hardness of tablets was found to be 7.0 (kg/cm^2) and drug release is only 74.25% in the buffer medium. Due to low drug release initially, if coated, this will tend to decrease more and fails the limits.

So, the subsequent trial is taken with the improvement in solubility. In the formulation F2, with the incorporation of dibasic calcium phosphate (8.33%) and slightly increasing the percentage concentration of kaolin and starch, removing the lactose anhydrous from extra granular part, the hardness of tablets shows 6.5 (kg/cm^2) only a slight difference and drug release was found to be 79.20% in the buffer medium. In the formulation F3, the inclusion of 1% sodium lauryl sulphate as a wetting agent and lactose anhydrous (27%) and povidone (3%) where friability failed in this batch. In formulation F4, removing sodium lauryl sulphate and starch were removed instead of microcrystalline cellulose (20%), DCP (19%) and kaolin (25%) were added. The disintegration time was 6 mins 10 sec, a little faster when compared to the other three trials. In this trial, tablets friability has passed. The drug release was found to be better when compared with previous batches (85.95%). In this trial, many materials stuck to the meshes may be due to kaolin at increasing concentration.

In the formulation F5, lactose is removed, and starch (20%), microcrystalline cellulose (27%), Dibasic calcium phosphate (19%) and Kaolin (18%) were added, disintegration time was found to be 9 mins 50 sec, and drug release also reduced to 80.10% when compared to the previous trial. Since a harder tablet is formed in this trial, a further trial reduces the hardness.

In the formulation F6, sodium lauryl sulphate at 0.3% concentration and lactose (27%) were incorporated and microcrystalline cellulose was removed, where the tablets disintegration time was found to be 5 min 10 sec, a little improvement and the drug release was found to be 89.62%. Trial 6 show better dissolution in pH 7.4 buffer medium, hence keeping 'F6' as the base formula further trial is taken. In the formulation F7, the tablet shows good mechanical strength and the disintegrating time was found to be 2 min 17 sec. The drug release was 93.98% in pH 7.4 phosphate buffer medium.

In all the formulations from F1 to F7, croscarmellose sodium was used as the disintegrant, and povidone K-30 was used as a binder. Based on disintegration time and drug release values observed for the various formulations, F7 shows good disintegration time and drug release in the buffer medium.

F7 formulation core tablet shows satisfactory analytical results and hence decided to enteric coat the core tablet with 2% seal coating and 7% enteric coating with the polymethacrylic acid methyl acrylate as polymer.

Evaluation of Post-compression Parameters for Enteric Coated Tablet: The optimized formulation (F7) was subjected to coating with 2% seal coating with the hydroxypropyl methylcellulose 15-cps as polymer and 7 % enteric- coating with the polymethacrylic acid methyl acrylate as polymer. The results for the evaluated parameters are given in Table 12. The thickness of the tablet was found to be 3.14mm, and hardness was 4.0 kg/cm^2. The % drug content was 99.92% which is acceptable under the limits. The % drug release was 0.055% in the acid medium and 90.74% in the buffer medium, which is the permissible limit as per the monograph.

Comparative *Invitro* dissolution study: The *Invitro* dissolution profile of formulation (F7) and the innovator product were compared by calculating the differential factor (f1) and similarity factor (f2). The results were tabulated in Table 14, and the factors f1 and f2 were found to be 5.32 and 75.08, respectively, which is an acceptable limit. Hence the two products were considered as similarand comparable.

Stability studies: Accelerated stability studies were carried out for the optimized formulation (F7) enteric-coated tablets. Twenty tablets were packed in blister packing and loaded in the stability chamber for three months at 40˚C±2˚C / 75% RH±5% RH. The resulted data are given in Tables 15 and 16. No significant changes were observed in the physical parameters, drug release and drug content when stored at 40˚C±2˚C / 75% RH±5% RH for three months. The drug release was 88.68% in the buffer medium, and the drug content was 89.87%, satisfying the pharmacopoeial limits. Hence it is concluded that the formulated enteric-coated tablets were stable.

CONCLUSION

The present study involves designing and formulating the enteric-coated tablets of bisacodyl and complying with the invitro dissolution data as per BP specifications. Preformulation studies have been performed to study the nature of API and the compatibility of API with excipients by physical observation and FT-IR studies. The results showed no interaction between API and all the excipients selected. Enteric-coated bisacodyl tablets were successfully formulated by the wet granulation method using the preferred excipient with the required quantities. The prepared tablets were evaluated for both pre-compression and post-compression parameters. The results were found to be satisfactory with the pharmacopoeial specifications. Among all the batches, formulation (F7) is the best formulation that complies with all the pharmacopoeial specifications. The best formulation is selected based on the in-vitro dissolution data compared with innovator products using the similarity factor. The most satisfactory formulation has been subjected to Accelerated stability studies as per ICH guidelines for three months at 40˚C±2˚C / 75% ±5% RH. The results of stability studies show no significant changes in the physical parameters of the tablets, drug content and in-vitro dissolution data until the end of 3 months from the initial values. Hence it is concluded that the formulated bisacodyl enteric-coated tablets were stable, and this study fulfilled all the pharmacopeial specifications.

REFERENCES

1. Hussan DS, Santanu R, Bhandari V. A review on recent advances of entericcoating. IOSR J Pharm. 2012;2(6):5-11.
2. Harshna P, Solanki N S. Gastro Resistant Drug Delivery System: A Review; International Journal of Drug Development & Research. 2012;4(4):1-8.
3. Sahitya G, Krishnamoorthy B, Muthukumaran M. Importance of Preformulation Studies in Designing Formulations for Sustained Release Dosage Forms, International Journal of Pharmacy and Technology. 2012;5(2):276-84.

4. Ummadi S, Rao R. Overview on Controlled Release Dosage Form. Int. J. Pharm. Sci. 2013;3(4):258-69.
5. Rowe CR, Sheskey P, Quinn M, editors, Handbook of Pharmaceutical Excipients, 6th ed; pg: 756-757.
6. Balamuralidhara V, Kumar P. Comparative Study of In-process and Finished Products Quality Control Tests of IP, BP and USP for Tablets: International Journal of Pharmacy Teaching & Practices. 2011;2(4):176-83.
7. Ankit G, Ajay B, Kumar MK, Neetu K. Tablet Coating Techniques: Concepts and Recent Trends. Int. Res. J. Pharm. 2012;3(9):50-53.
8. Ravi G, Subhash PCB, Ravi V, Saritha D, Srikanth PR, Sandeep K. Development and Evaluation of oral controlled release tablets of oxybutynin using various polymers. Res. J. Pharm. Tech. 2020;13(8):3854-60.
9. Allen LV, Popovich NG, Ansel CH. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 2011;9:185-91.
10. Rana SA, Kumar H. Manufacturing Defects of Tablets - A Review J. Drug Deli. Therapeutics. 2013;3(6):200-6.
11. Ravi G, Subhash PCB, Ravi V, Saritha D, Sandeep K. Design, Development and Evaluation of Isosorbide Mononitrate Orally Disintegrating Tablets. Int. J. Pharm. Res. Health Sci. 2020;8(2):3147-50.
12. Naresh A, Anil B, Yadav D, Garg A, Khanna S. A Review on development of HPMC Based Aqueous Enteric Coating Polymer. Int. J. Res. Pharm. Chem. 2012;2(3):570-4.
13. Peera HN. Formulation development and evaluation of oral disintegrating tablets of zolmitriptan. Der Pharmacia Lettre. 2013;5(2):324-32.

Cite this article as:

Srikanth Reddy *et al*. Formulation and evaluation of enteric-coated tablets of bisacodyl. Int. J. Res. Ayurveda Pharm. 2022;13(1):36-45 http://dx.doi.org/10.7897/2277-4343.13019

Source of support: Nil, Conflict of interest: None Declared