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Research Article

Effect of Lubricants on Properties of Conventional Tablets of Antihypertensive Drugs from Different Biopharmaceutical Classification System

Kavita Dindawar*[1], Supriya B.M.[2], Shivanand Kolageri[3],

[1,2] PES College of Pharmacy, Bengaluru, Karnataka.

[3]BLDEA's SSM College of Pharmacy and Research Centre, Vijayapur, Karnataka -India

A B S T R A C T

Background: Hypertension is a long-term medical condition in which blood pressure in the arteries is elevated. Hypertension causes coronary artery disease, stroke, heartfailure; kidney diseases etc.to over come hypertension, antihypertensive drugs are used.

Objectives: The aim of present work was to find out effectsof lubricants on properties of conventionaltablets containing antihypertensive drugs from different BCS class. Antihypertensive drugs suchas Metoprolol succinate, and Atenolol were selected which represented BCS class I, and II respectively.

Methods: Lubricants are the essential components of all solid dosage forms. Sodium stearyl fumarate, a hydrophilic lubricant was compared with Magnesium stearate,a conventional hydrophobic lubricant. Uncoatedtabletswereprepared either by direct compression or wet granulation technique employing sodium stearyl fumarate or magnesium stearate as a lubricant at 1% or 2%, mixing time of lubricants was varied as 3 and 6mins.

Results: Irrespective of class of drug, concentration, mixing time and processing method sodium stearyl fumarate turned out to be effective as tablet lubricant than Magnesium stearate. Both the Lubricants, when used at lower concentration and shorter mixing time resulted in superior tablets properties.Direc tcompression method gave better results than wet granulation technique. Both Sodium stearyl fumarate and Magnesium stearate (1%, 3min) were subjected to storage at40^0± 2^{0}C/ 75% RH for 90 days to check effect of aging and storage.

Conclusion: According to at the end of storage period up on investigating for different tablet properties there were no significan tchanges observed.

Keywords: Metoprolol Succinate, Nifedipine, Atenolol, Furosemide and Sodiumstearyl fumarate, Magnesium stearate.

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*Address for Correspondence:
Kavita Dindawar, PES College of Pharmacy WHR3+GJ2, 50 Feet Main Rd, Mysore Bank Colony, Hanumanthnagar, Banashankari 1st Stage, Banashankari, Bengaluru, Karnataka 560050

INTRODUCTION:

Metoprolol succinate extended-release tablets are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol.Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. Metoprolol is a beta-1 (cardioselective) adrenoreceptor-blocking agent. It was

first introduced as a tartrate salt and had pharmacokinetic/pharmacodynamic properties that necessitated twice- to thrice-daily dosing. This formulation is commonly referred to as "immediate release". Metoprolol was subsequently formulated as an extended-release tablet (metoprolol ER) using the succinate salt such that 95 mg is equivalent to 100 mg of the metoprolol. [1-5]

The metoprolol ER properties are achieved by encapsulation of the succinate salt with a polymeric coating to form micro-beads, which are then embedded in a tablet matrix. In the gastrointestinal tract the beads are released from the matrix and each bead, upon exposure to fluid, allows outward diffusion of metoprolol over a period of about 20 hours. [6-11]

Since lubricants have varying effect on different classes of drugs, the under-taken study aims toobserve the effects of different lubricants, their concentrations and duration of mixing on anti-hypertensive drugs from each class of the BCS, when the drug is formulated as a tablet dosageform.

Hypertension is a long-term medical condition in which blood pressure in the arteries is elevated. Hypertension causes coronary artery disease, stroke, heart failure; kidney diseases etc. to over come hypertension, antihypertensive drugs are used. Antihypertensive drugs are categorized as diuretics, calcium channel blockers, ACE inhibitors, vasodilators,[12-18]etc.

MATERIALS AND METHODS:

Chemicals and Reagents:

Metoprololsuccinate, Atenolol, obtained from Alembic Pharmaceutical Ltd. Vadora.

Magnesiumstearate, Lactose Potassiumdi-hydrogenorthophosphate, Di-sodium hydrogen orthophosphate, was obtained from Sisco research laboratories, Mumbai. All other chemical were purchased from Hi Media, Mumbai.All solvents and reagents were of analytical grade.

Determination of λ max: (Metoprolol succinate):

Metoprolol succinate was dissolved in a small quantity of 0.1NHCL and further diluted with the same to 100 ml. The drug solution was scanned for maximum absorbance in UV-visibledouble beam spectrophotometer (Shimadzu 1800) in the range from 200 to 800 nm. The λ max was found to be 222nm.

Determination of λ max: (Atenolol): Atenolol was dissolved in a small quantity of 0.1N HCL and further diluted with same to 100ml. The drug solution was scanned for maximum absorbance in UV-visible double beam spectrophotometer (Shimadzu 1800) in the range from 200 to 400 nm. The λ max was found tobe224nm.

Preparationof standardcurveformetoprololsuccinatein 0.1NHCL

- 100 mg of the drug was weighed and dissolved in 100 ml of 0.1N HCL to make stocksolutionS1 (1000 mg/ml)
- 10ml solution was withdrawn from S1 and volume was made up to 100ml (100 mcg/ml) with 0.1N HCL.
- From this secondary stock solution, aliquots of 5ml to25 ml were transferred into a series of 100ml volumetric flasks and final volume was made up with 0.1N HCL to give concentration in range of 5-25mcg/ml.
- The absorbance of these solutions was measured against a 0.1N HCL as blank in UV/visible spectrophotometer at 222nm. Average of three determinations was taken.

Preparationof standardcurveforatenololin 0.1NHCL

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- The absorbance of these solutions was measured against a 0.1N HCL as blank inUV/visible spectrophotometer at 224nm.Average of three determinations was taken.

Preparation of Tablet:

Direct compression method: Drug and all excipients were passed through sieve#80for further processing. Weighed quantities of drugs, other excipients and lubricants were thoroughly mixed in a polybag for 3 or 6 minutesto get a uniform blend of ingredients. The prepared powder blend was directly compressed on 8mm single station tableting machine.

Wet granulation method: The powder blend was prepared similarly to the first process. Later granules were prepared byusing potato starch solution as binder. Wet mass was passed through sieve #12 and dried at 60degree celsius for 30 min in hot air oven. Granules aremixed with lubricants in apolybagfor 3minand 6 min and compressed on 8mm single station tableting machine.

In vitro Disintegration Time (Metoprolol succinate and Atenolol)

The disintegration test was carried out using USP Disintegration Test Apparatus type-II. Sixtablets were placed individually in each tube of disintegration test apparatus and discs wereplaced over each tablet.0.1N HCL was usedas the medium maintained at 37°C ± 0.5°C andthetimetaken for eachtablet to disintegratecompletelywasrecorded.

Drugcontent: Drug content was determined by crushing the tablet in a glass mortar and pestle and extractingthe drug in suitable solvent (0.1Hcl- for metoprolol succinate and Atenolol, Phosphate bufferpH6.8- for Nifedipine and Furosemide) with continuous shaking on a rotary shaker for 24hrs.Drug content in each extracted fluid was assayed using UV spectrophotometer at respective nmagainstsuitableblank.

Drug content (Metoprolol succinate and Atenolol)

The prepared tablets were tested for their drug content. 3 tablets of each formulation were finelypowdered, powder equivalent to 100 mg of drug was accurately weighed and

the drug wascompletely extracted with 0.1N HCL and the solution was filtered. 1 ml of the filtrate was suitably diluted with 0.1NHCL and analyzed for drug content byUVspectrophotometer at 222nm and 235nm for Metoprolol succinate and Atenolol Respectively.

In-vitro dissolution study :(Metoprolol succinate and Atenolol)

In the present study the drug release was determined by USP type 2 dissolution apparatus. The dissolution medium was 900 ml 0.1N HCL (maintained at 37°C ± 5°C).at temperature and rotated at 50 rpm, 5 ml of the aliquot was withdrawn at regular interval time and replaced with fresh medium. Absorbance was noted at 222nm and 224nm for Metoprolol succinate and Atenolol Respectively.

Aging and storage studies on optimized formulations:

Optimized formulations were stored at 40±2^{0}C and 75%±5% RH for a period of 90 days. Atthe end of specified period tablets were evaluated for tablet properties including invitro drugrelease.

Effects of concentration of lubricants on tablet properties:

Tablets were prepared by direct compression method using Sodium stearyl fumarate or magnesium stearate at 1% and 2%w/w, mixing time was kept 3min

Table 1: Metoprolol succinate

Sl.no	Ingredients	Quantity in mg			
		1%	2%	1%	2%
		MS1	MS2	MM1	MM2
1	Metaprolol succinate	25	25	25	25
2	MCC	70	70	70	70
3	Lactose	70	70	70	70
4	PVPK30	20	20	20	20
5	Sodiumstarchglycolate	9	9	9	9
6	Aerosil	4	2	4	2
7	Magnesiumstearate	-	-	2	4
8	Sodiumstearylfumarate	2	4	-	-
Total weight of tablet		200	200	200	200

Table.2: Atenolol

Sl.no	Ingredients	Quantity in mg			
		1%	2%	1%	2%
		AS1	AS2	AM1	AM2
1	Atenolol	25	25	25	25
2	MCC	70	70	70	70
3	Lactose	70	70	70	70
4	PVPK30	20	20	20	20
5	Sodiumstarchglycolate	9	9	9	9
6	Aerosil	4	2	4	2
7	Magnesiumstearate	-	-	2	4
8	Sodiumstearylfumarate	2	4	-	-
Total weight of tablet		200	200	200	200

Effect of time of mixing on tablet properties:

Tablets were prepared by direct compression method using Sodium stearyl fumarate or magnesium stearate at 1% w/w, mixing time was varied as 3min and 6mins.

Table 3: Metaprolol succinate

Sl No.	Ingredients	Quantity in mg			
		3min	6min	3min	6min
		MS1	MS3	MM1	MM3
1	Metaprolol succinate	25	25	25	25
2	MCC	70	70	70	70
3	Lactose	70	70	70	70
4	PVPK30	20	20	20	20
5	Sodium starch glycolate	9	9	9	9
6	Aerosil	4	4	4	4
7	Magnesium stearate	-	-	2	2
8	Sodium stearyl fumarate	2	2	-	-
Total weight of tablet		200	200	200	200

Table.4: Atenolol

Sl No.	Ingredients	Quantityinmg			
		3min	6min	3min	6min
		AS1	AS3	AM1	AM3
1	Atenolol	25	25	25	25
2	MCC	70	70	70	70
3	Lactose	70	70	70	70
4	PVPK30	20	20	20	20
5	Sodium starch glycolate	9	9	9	9
6	Aerosil	4	4	4	4
7	Magnesium stearate	-	-	2	2
8	Sodium stearyl fumarate	2	2	-	-
Total weight of tablet		200	200	200	200

Effects of processing method on tablet property:

Tablets were prepared by wet granulation technique employing sodium stearyl fumarate as lubricant at 1%w/w concentration and mixing time 3mins.

(Potato starch was used as binder at 5% (10mg) concentration to the tablet weight and is added as mucilage. mucilage is prepared using water and used when it was fresh.)

Table 5: Metoprolol succinate/Atenolol

Sl. No.	Ingredients	Wet granulation(Quantity in mg)
		MSW/ASW
2	Metoprolol succinate/Atenolol	25
3	MCC	70
4	Lactose	70
5	PVPK30	20
6	Sodium starch glycolate	9
7	Aerosil	4
8	Sodium stearyl fumarate	2
Total weight of the tablet		200

RESULTS AND DISCUSSION:

Pre-formulation Studies:

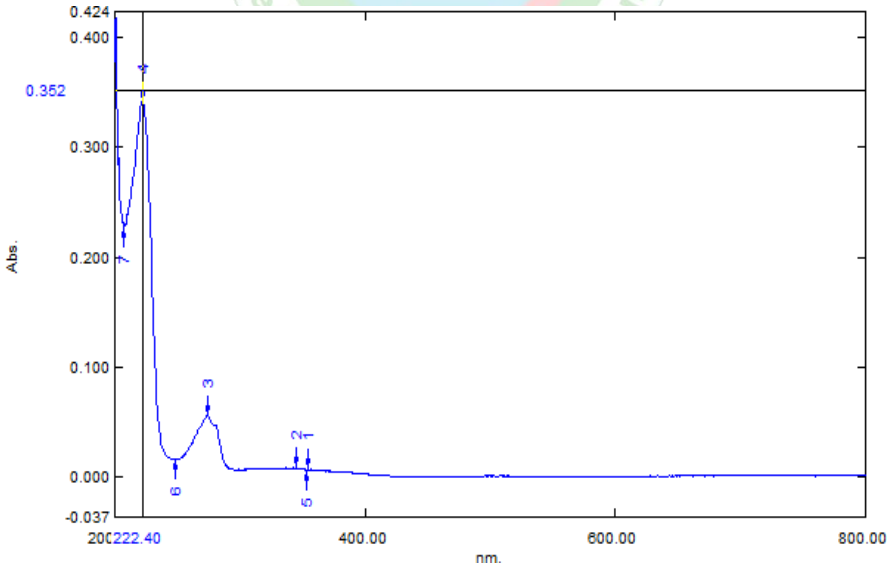

Figure 1: Selection of wavelength for metoprolol succinate: λ max was found to be 222nm

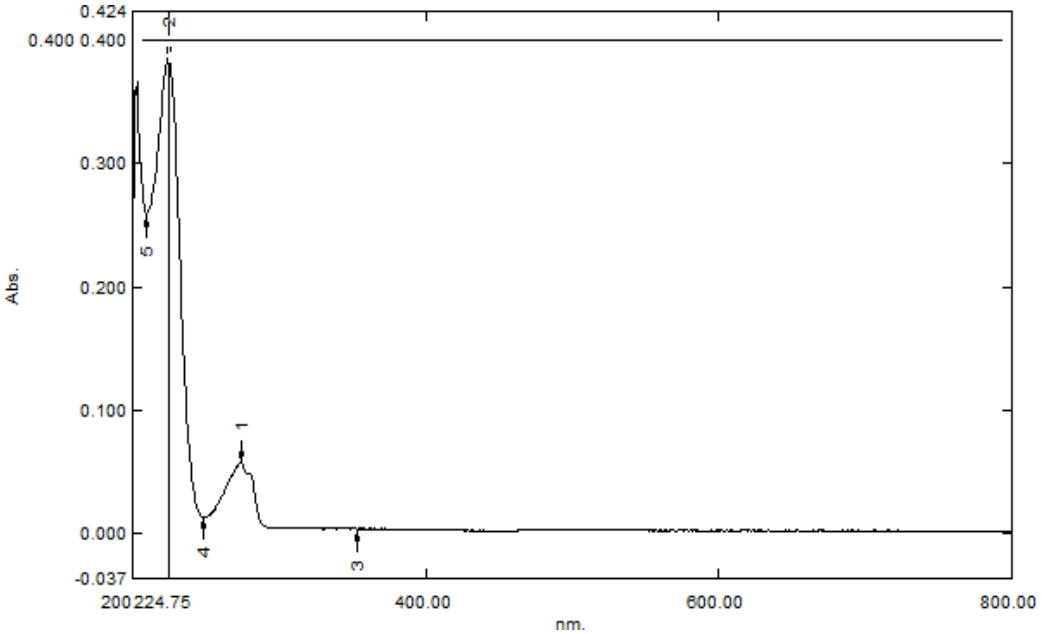

Figure 2: Selection of wave length for Atenolol: λ max was found to be 224 nm

Effect of concentration of lubricant:

Effect of lubricant on concentration tablet properties:

Flow properties of powder have inverse relationship with lubricant concentration. At lower concentration they showed excellent flow property and at high concentration they exhibited good flow property. Anti-adherent performance of both lubricants turned out to be sufficient as no sticking of powder to the funnel surface was observed. The increased lubricant level may have been responsible for the reduction in the inter particulate friction. This resulted in closer particle packing and densification. Thus, impending the flow ofpowderthrough thefunnel office.

Excellent flow property for powder with different lubricants had found in the order SSF > MS. Hardness decreased slightly with increase in concentration of SSF where as hardness value sharply decreased with increase in concentration of Magnesium stearate. Average disintegration time for Sodium stearyl fumarate tablets were 3.17 mins. And for Magnesium stearate tablets were 4.32 mins.The greater amount of drug released from SSF tablets than from Magnesium stearate tablets.

This happened because Sodium stearyl fumarate is inert, hydrophilic lubricant and does not retard the drug dissolution rate. Because of its greater water penetration capacity then Magnesium stearate it released drug more effectively. Magnesium stearate has the tendency to coatthe individual particlesandhence determined effects of this lubricant can be exacerbated.

Table.6 : Metoprolol Succinate drug and Atenolol

Pre-compression parameter	Formulation code							
	MS1 (1%)	MS2 (2%)	MM1	MM2	AS1 (1%)	AS2 (2%)	AM1 (1%)	AM2 (2%)
Bulk density (g/cc)	0.68	0.65	0.63	0.6	0.81	0.79	0.74	0.71
Tapped density (g/cc)	0.75	0.73	0.72	0.69	0.86	0.85	0.77	0.75
Compressibility Index (%)	9.4	11	12.5	13.1	3.9	5.4	5.9	7.1
Hausner'sRatio	1.1	1.12	1.14	1.15	1.04	1.05	1.06	1.07
Angleofrepose (θ)	19	20.2	19.6	20.3	20.3	21.8	21.06	22.5

Evaluation of post-compressive parameters

Table 7: Metoprolol Succinate drug and Atenolol

Post Compression parameter	Formulation code							
	MS1 (1%)	MS2 (2%)	MM1 (1%)	MM2 (2%)	AS1	AS2	AM1	AM2
Weight variation	201±0.03	199±0.03	202±0.02	198±0.031	197±0.02	198±0.01	200±0.08	201±0.025
Hardness (kg/cm^2)	5.7	5.5	6.6	5.8	5.4	5.2	6.7	5.9
Friability (%)	0.38	0.42	0.32	0.36	0.43	0.45	0.32	0.35
Disintegration time(min)	2.58	3.18	4.16	4.32	2.56	3.17	4.08	4.23
% Drug content	97.3±0.3	94.8±0.26	93.4±0.4	91.6±0.5	96.3±0.23	90.3±0.2	87±0.2	84.32±0.25

Table 8: *In-vitro* Drug Release: Prepared Metoprolol Succinate drug and Atenolol

Time (min)	Formulation							
0	**MS1 (1%)**	**MS2 (2%)**	**MM1 (1%)**	**MM2 (2%)**	**AS1**	**AS2**	**AM1**	**AM2**
5	0	0	0	0	0	0	0	0
10	25.6	18.64	24.2	17.67	14.93	10.31	13.64	9.61
15	44.21	41.94	39.8	36.34	29.93	24.26	27.17	18.81
20	65.12	52.3	59.86	49.2	47.38	40.12	42.3	39.68
25	74.4	68.1	65.02	56.38	70.2	58.9	67.52	57.35
30	91.73	80.1	81.8	73.25	78.74	73.59	74.34	71.55
	96.88	93.77	91.76	85.6	87.55	81.72	85.31	80.53

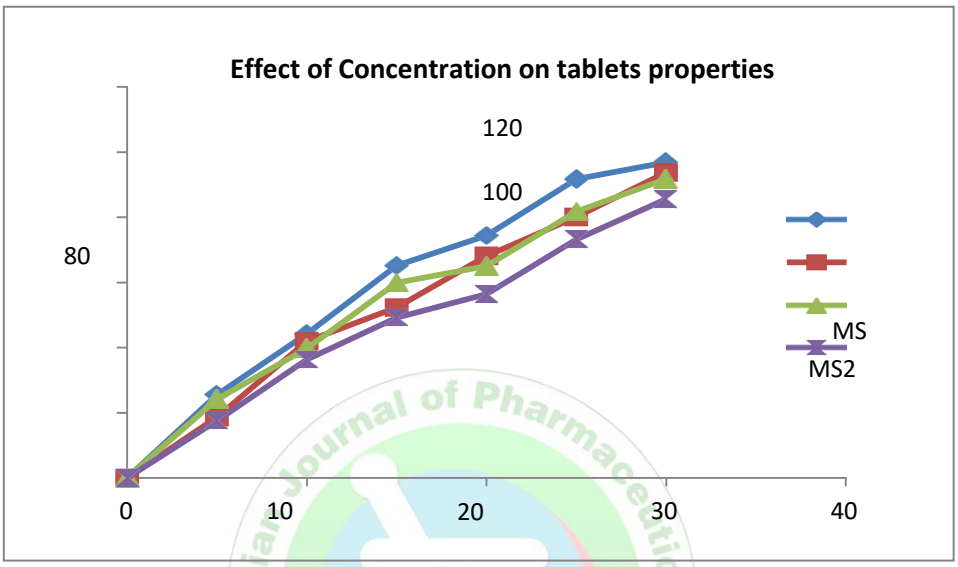

Figure 3: Effect of Concentration on tablets properties

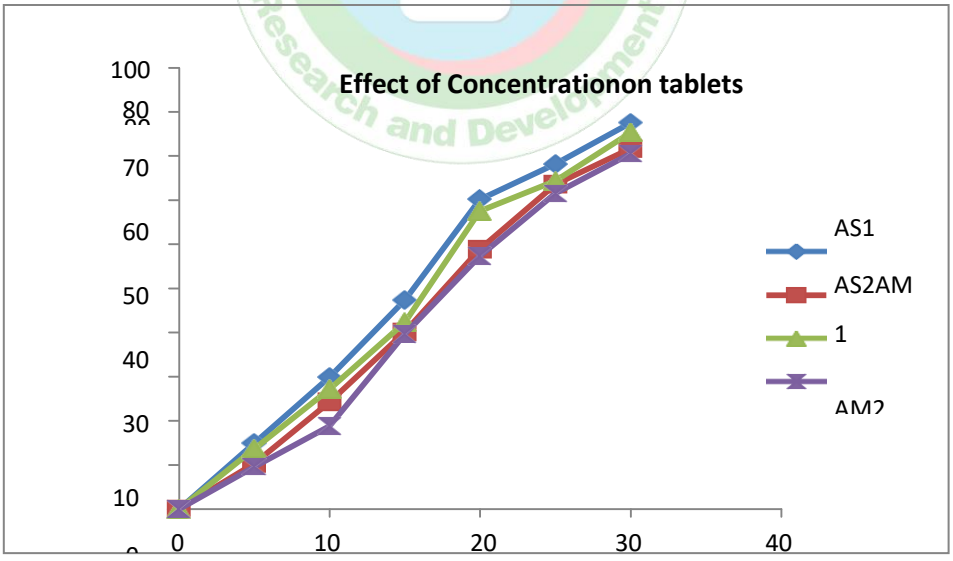

Figure 4: Effect of Concentration on tablets properties

Effect of mixing time:

Evaluationofpost-compressionparameters

Effect of time of mixing on tablet properties: The change with Magnesium stearate is due to reduction in the physical strength of tablets which inturn because the of formulation of this lubricant film around each drug particle during blending. This physical barrier weakens the strong inter particulate bonding. In addition to decreased bonding properties the wettability due to its pronounced hydrophobic nature can cause delayed disintegration and prolonged dissolution rate. No change in disintegration time was observed with Sodium stearyl fumarate therefore SSF appearsto beagood alternativetomagnesium stearate.

Table: 9

Postcompression parameter	Formulation code							
	MS13 min	MS 36min	MM 13min	MM 36min	AS 13min	AS 36 min	AM 13 min	AM 36min
Weight variation	201± 0.0 15	202±0.03	199±0.002	198±0.001	197±0.03	199±0.021	201±0.04	198±0.01
Hardness (kg/cm^2)	5.2	4.9	5.5	5.3	5.3	4.8	5.8	5.4
Friability (%)	0.41	0.45	0.38	0.4	0.39	0.43	0.36	0.41
Disintegration time(min)	2.51	3.09	3.19	3.27	3.1	3.28	3.46	4.02
% Drug content	92.2 ± 0.12	96.3±0.24	95.3±0.31	93.1±0.33	96.1±0.16	93.3±0.22	93.36±0.26	90.2±0.4

Table 10: *In-vitro* drug Release

Time(min)	Formulation							
	MS13 min	MS 36 min	MM 13 min	MM 36 min	AS 13 min	AS 36 min	AM 13 min	AM 36 min
0	0	0	0	0	0	0	0	0
5	24.8	17.34	19.8	14.75	14.8	12.62	13.38	10.2
10	41.6	39.08	43.61	35.36	27.06	22.13	24.6	18.63
15	63.2	58.6	62.43	38.68	52.81	45.3	46.28	38.96
20	71.95	69.35	70.02	50.32	68.63	61.23	65.73	55.81
25	88.65	87.56	87.7	72.3	85.42	73.36	76.29	72.18
30	95.31	93.06	94.89	88.35	94.73	89.94	91.64	87.29

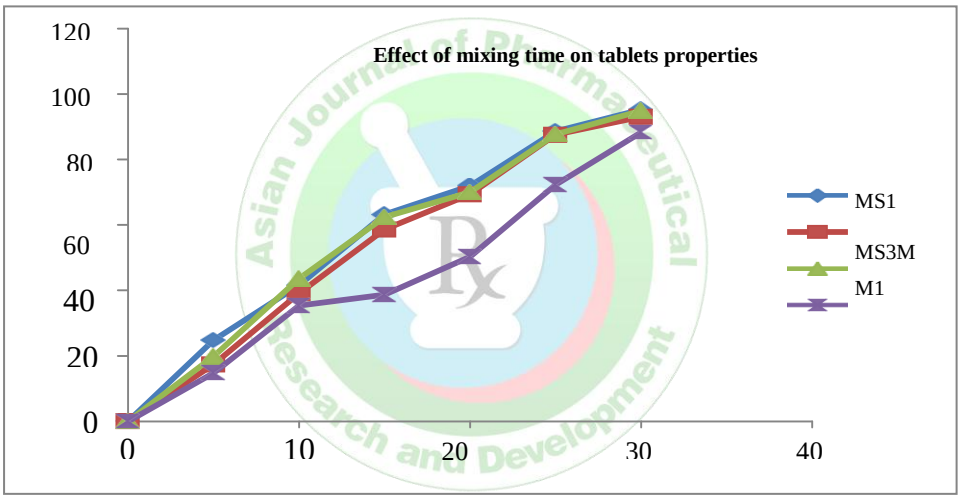

Figure 5: Effect of mixing time on tablets properties

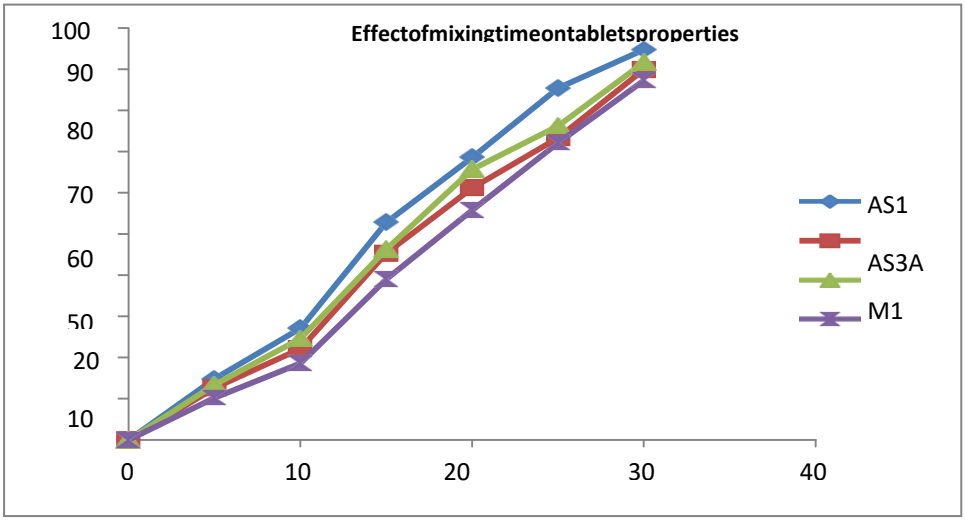

Figure 6: Effect of mixing time on tablets properties

Effect of tablet processing method:

Evaluation of post compression parameters:

Tablet hardness is a function of compressive load, Granule or crystal hardness, Different excipients used and their concentration Starch paste was used as a binder in wet granulation tablets. Additionally, MCC produces rapid even wetting by wicking throughout the powder blendthus facilitating function of harder tablets. Higher values of hardness for wet granulation tablets can also be attributed to the formulation of liquid bridges with subsequent crystallization and hardening of adhesive by drying.

Decreased friability with wet granulated tablets because of improved bonding upon compression due to the presence of MCC being completely devoid of moisture in direct compression tablets of ten produce more friable tablet.

Wet granulation tablets showed longer disintegration time than that of directly compressed tablets. This can be due to higher hardness of wet granulated tablets. Inherent disintegration property of Avicel itself and absence of additional binders played an important role in shorter disintegration time of directly compressed tablets.

In case of dissolution, it was found that slower release of drug from wet granule tablets, alongwith solid liquid bridging by binders, and wet granulation may create hydrated form of drug which was less soluble thereby causing reduction in drug releaserate.

Table.11

Post compression parameter	Formulation code							
	MS1 (DC)	MSW	MM1 (DC)	MMW	AS1 (DC)	ASW	AM1 (DC)	AMW
Weight	201±0.03	201±0.032	202±0.02	198±0.015	197±0.02	198±0.03	200±0.08	201±0.01
Hardness (kg/cm^2)	5.7	5.9	6.6	6.8	5.4	5.8	6.7	6.9
Friability (%)	0.38	0.33	0.32	0.29	0.43	0.36	0.32	0.29
Disintegration time (min)	2.58	3.49	4.16	4.23	2.56	3.38	4.08	4.19
% Drug content	97.3±0.3	95.1±0.2	93.4±0.4	89.3±0.5	96.3±0.23	94.28±0.23	87±0.2	85.3±0.21

Table 12: *In vitro* drug release:

Time(min)	Formulation							
	MS1 (DC)	MSW	MM1(DC)	MMW	AS1(DC)	ASW	AM1(DC)	AMW
0	0	0	0	0	0	0	0	0
5	25.6	23.1	24.2	23.3	14.93	11.62	13.64	12.16
10	44.21	40.6	39.8	37.60	29.93	25.21	27.17	25.92
15	65.12	61.3	59.86	58.16	47.38	43.36	42.3	40.83
20	74.4	70.28	65.02	63.43	70.2	66.5	67.52	66.34
25	91.73	88.63	81.8	79.56	78.74	73.56	74.34	73.03
30	96.88	92.71	91.76	89.09	87.55	82.19	85.31	83.81

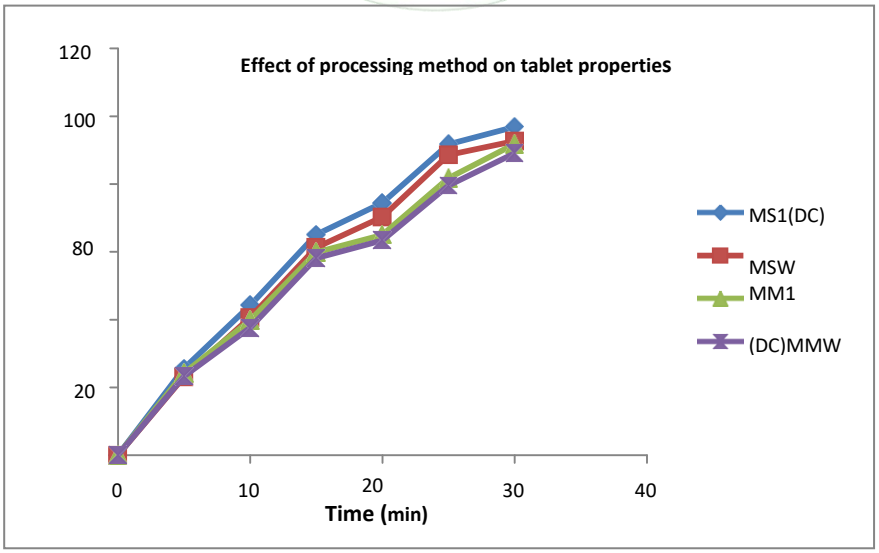

Figure: 7: Effect of processing method on tablet properties

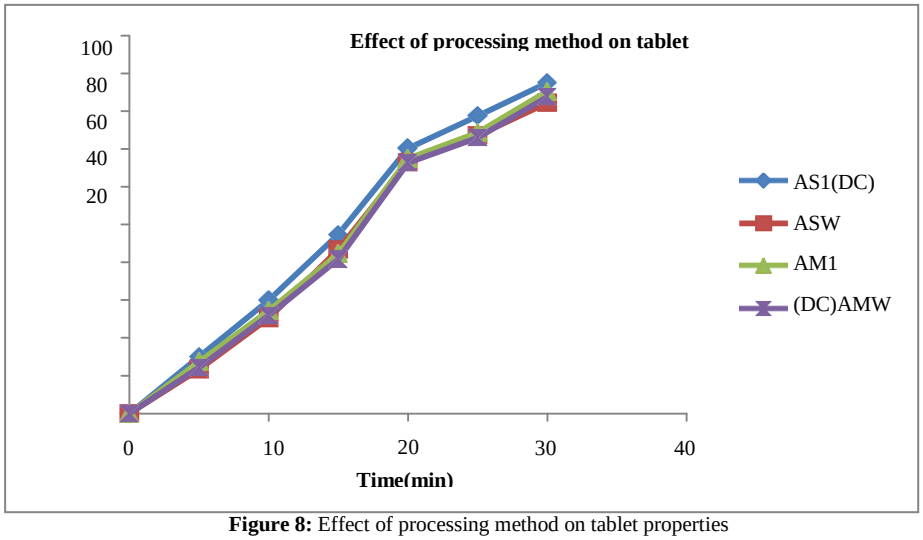

Figure 8: Effect of processing method on tablet properties

Effect of aging and storage:

Table 13: Evaluation of post-compression parameters

Post compression parameter	Formulation code							
	MS1 (initial)	MS1 (3 month)	MM1 (initial)	MM1 (3 month)	AS1 (initial)	AS1 (3 month)	AM1 (initial)	AM1 (3 month)
Weight variation	201±0.03	200±0.01	202±0.02	201±0.03	197±0.02	196±0.1	200±0.08	199±0.06
Hardness (kg/cm^2)	5.2	5.13	5.5	5.42	5.3	5.1	5.8	5.6
Friability (%)	0.38	0.36	0.32	0.31	0.43	0.40	0.32	0.29
Disintegration time (min)	2.51	2.56	3.19	3.21	3.1	3.33	3.46	3.49
% Drug content	98.2±0.12	97.6±0.2	95.8±0.31	94.62±0.25	96.1±0.16	95.62±0.1	93.36±0.26	92.45±0.25

Table.14: *In-vitro* Drug Release

Time (min)	Formulation							
	MS1 (initial)	MS1 (3month)	MM1 (initial)	MM1 (3month)	AS1 (initial)	AS1 (3month)	AM1 (initial)	AM1 (3month)
0	0	0	0	0	0	0	0	0
5	24.8	24.3	19.8	19.2	14.8	14.21	13.38	12.8
10	41.6	40.41	43.61	42.47	27.06	26.53	24.6	23.24
15	63.2	62.05	62.43	61.12	52.81	51.06	46.28	45.83
20	71.95	70.8	70.02	69.32	68.63	67.3	65.73	64.29
25	88.65	87.2	87.7	87.1	85.42	84.62	76.29	75.69
30	95.31	94.6	94.89	93.81	94.73	93.26	91.64	90.05

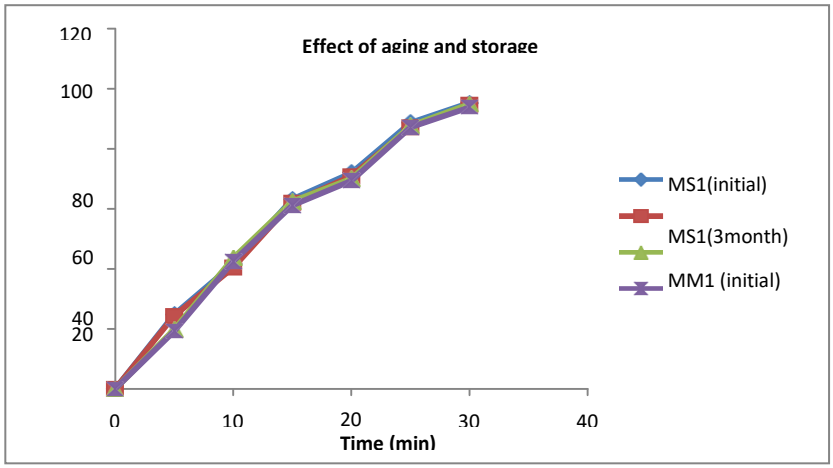

Figure 9: Effect of aging and storage property

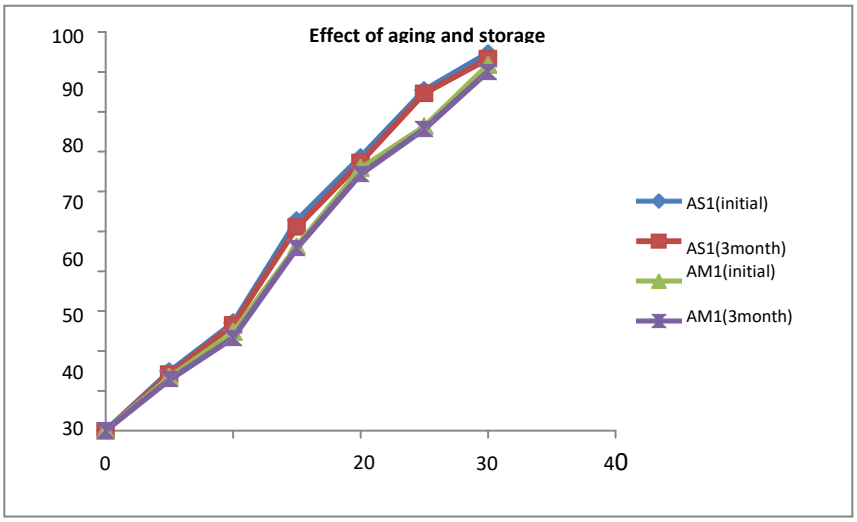

Fig.10: Effect of aging and storage property

DISCUSSION:

Metoprolol succinate is an antihypertensive drug (beta-blocker) belonging to BCS class 1 (high solubility and high permeability) and is available in the market as oraltablets. Atenolol is an antihypertensive drug (selective beta1 receptor antagonist) belonging to BCS class3 (High solubilityand lowpermeability)and is available inmarket as oral tablet. The present study was taken up to formulate tablet dosage form and evaluate the effects oflubricant on properties of conventional tablets of antihypertensive drugs from different BCSclass.

In the present work an attempt was made to find out the influence of type, concentration andmixing time of lubricant which gives better results for tablets when drugs of different class were used. The tablets were prepared by direct compression or wet granulation method using hydrophilic (SSF) or hydrophobic (Mg.St) lubricant at two different concentrations (1% and 2% w/w) and mixing time (3 and 6 mins). The prepared tablets were subjected to pre and post-compression evaluation in order to determinethe effect of lubricant and process variables on properties of tablets including in vitro releaseprofile.

CONCLUSION:

For compaction of tablet formulation containing drug from any BCS class SSF can be used as efficient lubricant. At lower concentration and shorter mixing time both the lubricants i.e., SSF and magnesium stearate showed excellent flow property.

Increased concentration and mixing time of lubricant was found to reduce flow property of powder in terms of carr's index.

Tablets made by direct compression method were more effective than wet granulation technology in terms of direct compression and release of drug.

LIST OF ABBREVIATIONS:

BCS- Biopharmaceutical classification system

SSF- Sodium stearyl fumarate

mcg- Microgram

ml- milliliter

Mg- Milligram

IP-Indian Pharmacopeia

UV- Ultraviolet

Nm- Nanometer

ACE- Angiotensin-converting enzyme

MCC- Microcrystalline cellulose

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CONFLICT OF INTEREST:

The authors declare that no financial or commercial ties that might be viewed as creating a conflict of interest existed throughout the research.

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