Consequences related to change in compaction pressure and microcrystalline cellulose concentration in amlodipine immediate release tablets along with croscarmellose sodium: a guide to modify the release

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Abstract

Background: Amlodipine besylate is well known for its hypertensive property and its effectiveness against coronary artery diseases. Microcrystalline cellulose (MCC) and croscarmellose sodium (CCS) are well known for their disintegration properties. Our objective is to ilucidate the effect of different concentration of MCC along with CCS as super disintegrant at different pressure in order to achieve amlodipine immediate release tablets.**Methods:**The tablet was formulated by using croscarmellose sodium, lactose, talc, magnesium stearate at constant concentration and with varying concentration of MCC (i.e 50%, 33.33%, 25%, and 0 %). Parameters like thickness, hardness, friability, water uptake, swelling index, drug content, tensile strength, in-vitro disintegration and in-vitro dissolution profile of all formulated tablets were evaluated. In-silico docking study was performed to forecast the binding interaction between MCC and amlodipine. **Results:** By increasing the % of MCC the disintegration time was found to decrease. Both the formulation containing 33.33% and 50% of microcrystalline cellulose showed almost similar drug release profile hence 33.33% of MCC containing formulation was selected for further inquiry. The screened formulation (i.e 33% MCC) was again analysed to verify the effect of pressure (1, 2, 3 and 4 ton) on the formulation through different aspects. The tablets were prepared by applying one ton pressure showed better swelling index, water uptake, disintegration time and drug release

profile. This might be due to the water retention capacity of micro crystalline cellulose and less pressure which helped in swelling and further disintegration. **Conclusions:** So it could be a superior strategy towards designing amlodipine immediate release tablet by using MCC (33.33%) along with CCS by applying one ton pressure.

INTRODUCTION

Amlodipine a long acting, third generation, lipophilic calcium channel antagonist (vasodilator) belongs to the 1, 4-dihydropyridine class is well established for its vascular selectivity and longer duration of action in the heart as antihypertensive, antianginal and for treating coronary artery disease (Zaid*et al.*, 2014; Fares *et al.,* 2016). It exerts its action through inhibition of calcium influx into vascular smooth muscle cells and myocardial cells which result in decreased peripheral vascular resistance (Fares *et al*., 2016). Quick action is demanded to tackle with the crucial time as these are all serious health conditions.

An immediate release oral tablet focuses on the availability of drug readily as short a time is possible. Immediate release tablets are designed to disintegrate within a maximum time of 60 seconds(Gaikwad, Kshirsagar, 2020; Trivedi, Siriah, Puranik, 2020). Superdisintegrants are adopted while designing an appropriate solid dosage form especially tablet dosage form for its ability to bring disruptive change in tablets. In addition to that it promotes compressibility even in high doses it does not reflect any negative impact on the mechanical strength of the formulation (Sharma, Pahuja, Sharma, 2019; Ramana, Murthy, 2018).Selection of excipient plays an imperative task behind immediate release dosage form. At the same time, it also determines the quality thereby the performance of the final formulation. The functionality of croscarmellose sodium (CCS) as superdisintegrant is related to fluid uptake and swellability characteristics also have swelling, wicking, and strain recovery properties. Hence CCS was taken in all the formulations to promote the disintegration. MCC 102 being a versatile excipient contributes as flowability aid, diluent, binder, disintegrant, and also can be used for enhancement of the liquid transport into a tablet matrix, accelerating both diffusion and capillary action (Thoorens*et al.*, 2015). The fibrous organization of MCC 102 makes it more appropriate in designing an immediate release tablet dosage form. Hygroscopicity and elastic deformation property of MCC 102 helps it to absorb more water into it, hence fastening the disintegration (Yassin*et al.*, 2015; Yadav, Kapoor, Bhargava, 2012). According to the index of good compression (IGC) MCC 102 shows better compressibility, flowability, stability, and lubricity for direct compression. MCC 102 presents

median particle size of 100mm and has already tested for its flow properties required for successful high speed tableting

MCC 102 was used instead of Silicified microcrystalline cellulose (SMCC 102) to formulate an economically sound formulation as SMCC 102 is comparatively costly. Compression force plays a vital role in designing a tablet because it can alter the crystalline structure of cellulose and can ultimately result in specific delay in dissolution , disintegration, and water absorption capacity. The reason behind targeting the oral route is to design a versatile formulation while emphasizing on patient compliance. Specifically, the tablet dosage form was chosen instead of the other due to its stability and acceptability (Aljaberi*et al.,* 2009).

Although amlodipine has tremendous effects but immediate action using CCS along with MCC 102 as superdisintegrant and effect of compression pressure on it remains suboptimal. This research work is concerned with the improvement of the disintegration rate of amlodipine as a tablet dosage form using MCC 102. The effect of MCC 102 in different concentrations and pressure has also been undertaken to understand the release modification of amlodipine tablets.

MATERIALS AND METHOD

Materials

Amlodipine besylate was collected as a gift sample from Concept Pharmaceutical Pvt.ltd. Aurangabad, India. Other excipients like microcrystalline cellulose, croscarmellose sodium, Talc, Magnesium stearate, and Lactose were procured from Merck Specialities Private limited, India.

Methods

Formulation of amlodipine besylate IR tablet

Four batches of amlodipine besylate IR tablets were prepared by taking amlodipine, CCS, talcum, and magnesium stearate. The percentage of MCC 102 used was varied (i.e. 50%, 33.33%, 25%, 0%), and to make the tablet weight of 150mg, lactose was used as a filler (Table I). All the excipients along with the drug were properly weighed followed by mixing. The powder mixture was allowed to pass through the sieve number 60 and dried at 50^0C for 30 minutes in a hot air oven and finally punched by using the hydraulic machine with 8mm

die punch by applying one ton pressure with a retention time of 5 minutes. The tablet containing 33.33% of MCC 102was again investigated by its performance with varying compression force (i.e. 1, 2, 3, 4 ton) (Table II). These processes were carried out in laboratory ambient conditions at 27^0C. \

TABLE I - Formulation of Amlodipine tablet with MCC 102 variation

Formulation code	Amlodipine (mg)	Croscarmellosesodium (mg)	Talcum (mg)	Magnesiumsterate (mg)	Microcrystalline cellulose (mg)	Lactose (mg)	Total weight of the tablet (mg)
F1	5	11.25	0.75	0.75	75	57.25	150
F2	**5**	**11.25**	**0.75**	**0.75**	**49.99**	**82.26**	**150**
F3	5	11.25	0.75	0.75	37.5	94.75	150
F4	5	11.25	0.75	0.75	0	132.25	150

TABLE II - Frmulation of optimized Amlodipine(F2) tablet with pressure variation

Formulation code	Amlodipine (mg)	Croscarmellose sodium (mg)	Talcum (mg)	Magnesiumsterate (mg)	Microcrystalline cellulose (mg)	Lactose (mg)	Total weight of the tablet (mg)	Pressure (ton)
F2	5	11.25	0.75	0.75	49.99	82.26	150	1
F5	5	11.25	0.75	0.75	49.99	82.26	150	2
F6	5	11.25	0.75	0.75	49.99	82.26	150	3
F7	5	11.25	0.75	0.75	49.99	82.26	150	4

Micromeritics properties of the powder mixture

As the powder carry many properties that illustrate certain behaviour as an outcome, so it is essential to identify its behavioural property. All the parameters like bulk density, tapped density, angle of repose, compressibility index or carr's index, and hausner's ratio were validated properly to ensure its powder property before formulating the formulation.

Evaluation of the formulated tablet

Physical evaluation

All these parameters are directly related to the dissolution and disintegration which can affect the formulation in terms of its quality and efficacy. Hence hardness and thickness of these tablets were verified using a digital hardness tester (Pfizer hardness tester) and digital micrometer (by verniercalipers) respectively. The friability was tested using Roche friabilator (Panomeximc; PX/FTA-202) and can be calculated by the following formula (Saleem *et al.*, 2014),

W (Initial)-W (final)/W (Final)*100 (Eq. 1)

Where W is the weight of the sample

Tensile Strength (TS) and Swelling index

Tensile strength (TS), one of the most important attribute which defines the strength to fracture the tablet specimen across the diameter (Juban*et al.*, 2017). The tensile strength was measured by the hardness tester following two methods the pressure and tapping method. The TS of the tablet (Pitt, Heasley, 2013) can be determined by following formula

$TS = 2F/\pi dt$ (Eq. 2)

Where.F is the crushing strength, d is the diameter, and t is the thickness of tablets

The swelling index portrays the disintegration and dissolution rate. So it was calculated by putting a dry tablet on a wet filter paper and the weight was checked before and after wetting for a period of 15, 30, and 75 sec. It was calculated (Chen *et al.*, 2015) by the following formula.

R = 100×Wa-Wb/Wb(Eq. 3)

Where Wa is the final weight of the hydrated tablet, Wb is the initial weight of the tablet

Disintegration test

Six tablets of each formulation were selected which were subjected to a disintegration test in distilled water at 37±2^{0}C using digital tablet disintegration test machine I.P.STD. (Ikon instrument). The tablets were allowed to dip inside the liquid surface up to 2.5 cm carefully followed by the upward and downward moment. The time taken for disintegration was recorded (Shoormeij*et al.,* 2017).

Drug content uniformity

It is important to confirm the uniform distribution of drug within the tablet to ensure the tablet contains appropriate dose to demonstrate its potency. For content uniformity clarification, ten random tablets were selected, weighed and average weight per tablet was calculated followed by trituration individually. Exactly weighed tablet powder equivalent to 10 mg drug was dissolved in 100 ml 0.01N hydrochloric acid and then filtered. From that filtrate 10µg/ml drug solution was prepared using 0.01N hydrochloric acid and the concentration was measured by UV visible spectrophotometer (Thermo scientific, Evolution 201-uv-visible spectophotometer) at 364 nm (Li, Castillo, 2020).

Differential scanning calorimetry (DSC)

Thermal analysis of the powder samples was carried out by differential scanning calorimetry (DSC-1, Mettler Toledo software) to understand the drug excipient interaction in the tablet formulation. The DSC was run in the range of 30-300^{0}C with a constant heating rate of 10^{0}C /minute under nitrogen gas purge. Sample taken for this analysis was 3-4mg (Trivedi*et al.,*2020).

Fourier transform-infrared spectroscopy

Fourier transform-infrared spectroscopy (FTIR) of the dried sample and the pure drug was carried out by using an FTIR spectrophotometer (Bruker alpha-II). Using the integrated pressure application mechanism on the Bruker infrared analyser, samples were placed on zinc selenide crystal and pressed onto the attenuated total reflectance crystal (ATR crystal). (Fernandes*et al.,* 2020).

X-ray diffraction

X-ray diffraction analysis was carried with pure amlodipine, MCC 102, and the screened formulation (F2) by X-ray diffractometer (Rigaku ultimate, PXDL software). For analysis 40kV voltage and 15mA as current was allowed to pass as a basis of X-ray anode material Cu, K-Alpha radiation 1.5406 Å was applied, in between the scanning angel 2Ɵ from 5 to 70^0. The measurements were taken at a scan speed of 1^0/ min (Nwachukwu*et al.,* 2020).

***Insilico* docking study of amlodipine and MCC 102**

Auto duck tools were used in the prediction of binding interactions between MCC 102 and amlodipine following Dash *et al.,* 2019.

***In vitro* dissolution test**

The dissolution study of each tablet was performed by using USP type II apparatus (rotating paddle type) introducing 500ml of 0.1N HCl as dissolution medium with a maintained temperature of 37^0C±0.5^oC. The baskets were operated at 50rpm for 30minutes. 5ml of the sample was withdrawn at the time interval of 2, 5, 7, 10, 12, 15, and 30 minutes followed by replacement of 5ml blank to each. The absorbance of the collected samples was measured by using UV Visible spectrophotometer at 364nm (Dash *et al.,* 2019, Anumolu*et al.,* 2014).

RESULTS AND DISCUSSION

Physical parameters

The outcome of bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio gave an assurance towards the processability of the tablet as all the results (Table III.) favoured by matching to the IP standard**.**

TABLE III- Micromeritics study of Amlodipine, MCC 102 and blend containing different proportions of MCC

Experiments	Amlodipine	MCC 102	Blend containing different proportions of MCC			
			F1	F2	F3	F4
Bulk volume (ml)	10.4±0.25	14.2±0. 18	11.4±0.28	11.2±0.19	10.8±0.25	10.2±0.27
Tapped volume (ml)	8.2±0.12	12.7±0.13	9.8±0.15	9.3±0.14	8.7±0.17	8.1±0.19
Angle of Repose (Ɵ)	34.82±0.37	20.92±1.09	24.53±0.42	25.68±0.58	28.4±0.35	30.15±0.47
Compressibility Index (%)	21.15±2.05	10.56±1.5	14.03±1.21	16.96±1.08	19.44±2.05	20.58±1.73
Hausner's Ratio	1.26±0.06	1.11±0.28	1.16±0.02	1.2±0.12	1.24±0.08	1.25±0.09

EVALUATION OF AMLODIPINE TABLET

Physical evaluation

The result of hardness, thickness, friability, disintegration time, and tensile strength of all the 7 formulations were tabulated in Table IV. Formulation with variation in MCC 102 concentration (F1-F4) showed an increase in disintegration time as the MCC 102 concentration decreased while a decrease in tensile strength was observed by increasing the MCC 102 concentration. Though there is no significant difference observed between F1 and F2 the formulation, so F2 with 33% MCC 102 and one ton pressure among the four variations was scrutinized for further pressure analysis. F5, F6, and F7 showed an increase in disintegration time and tensile strength with an increase in pressure to 2, 3, and 4 respectively. Hence to make sure the above release profile was compared further.

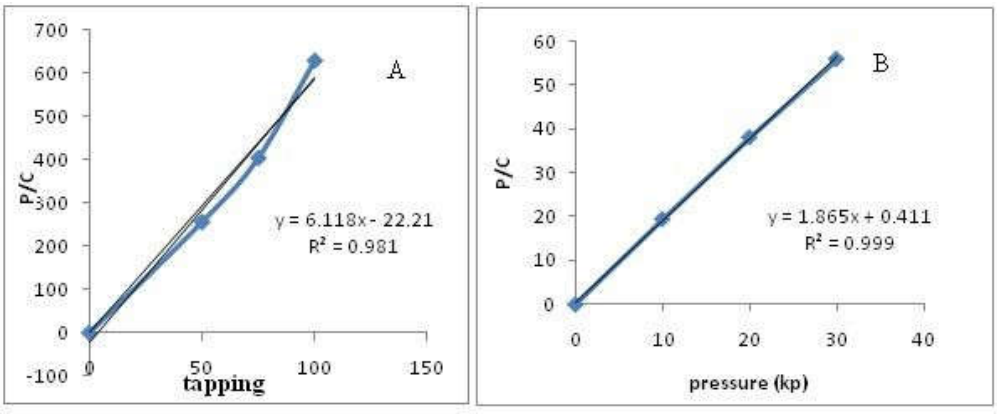
TABLE IV- Post compression parameters of F1 to F7

Formulation	Hardness (N)	Thickness (mm)	Friability (%)	Disintegration Time(sec)	Tensile strength (MPa)
F1	2 ±0.2	2.52	0.59	18	0.41
F2	2.1 ±0.07	2.54	0.62	20	0.39
F3	2.3 ±0.1	2.52	0.6	32	0.58
F4	2.2 ±0.21	2.53	0.42	43	0.95
F5	2.4 ±0.1	2.14	0.36	54	1.19
F6	2.8±0.32	2.09	0.32	61	1.29
F7	3.2±0.39	2.04	0.21	66	1.48

Tensile strength by pressure and tapping method

By applying the pressure on the powder bed the bulk volume was found to reduce with increasing bulk density. Tablet porosity was influenced by the reduction in the volume by tapping and applying pressure. The formulation F2 with 33.33% of MCC 102 and one ton pressure was found to have sufficient tensile strength, good porosity which was observed by both the tapping and pressure method (Figure 1).

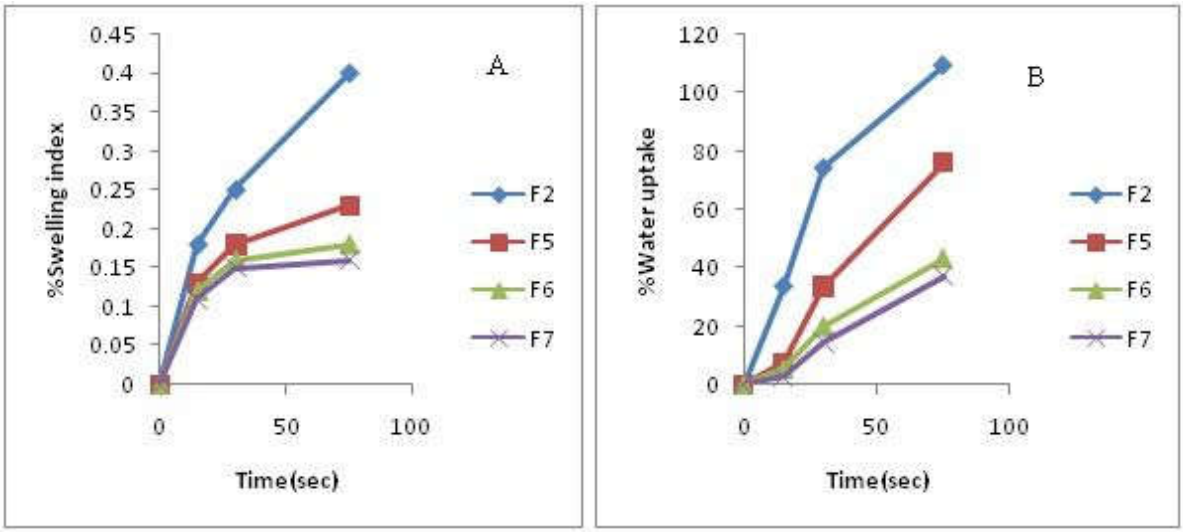
FIGURE 1 - Tensile strength of 33% MCC 102 (A) by tapping method, (B) by pressure method (one ton)



Swelling index and water uptake

The swelling index study exposed the swelling nature of tablets whereas water uptake revealed the percentage of water taken by the tablets. The formulation F2 was found to show maximum swelling (0.4%) and water uptake (105%) nature whereas F7 was showing least swelling (0.15%) and water uptake (32%) nature which is elucidated in the graph below (Figure 2). This might be due to the water retention capacity of MCC 102 and the pressure applied.

FIGURE 2 - (A) % of swelling of F2, F5, F6, F7 and (B)% of water uptake of F2, F5, F6, F7.



Disintegration test

The tablet containing 25% of MCC 102 showed 32 seconds for disintegration whereas the tablet containing 33.33% and 50% MCC 102 took 20 and 18 seconds to disintegrate (Table IV). An increase in concentration of MCC 102decreased the disintegration time which was concluded from the above cited data. The increased pressure reflected its response by simultaneously rising the disintegration time.

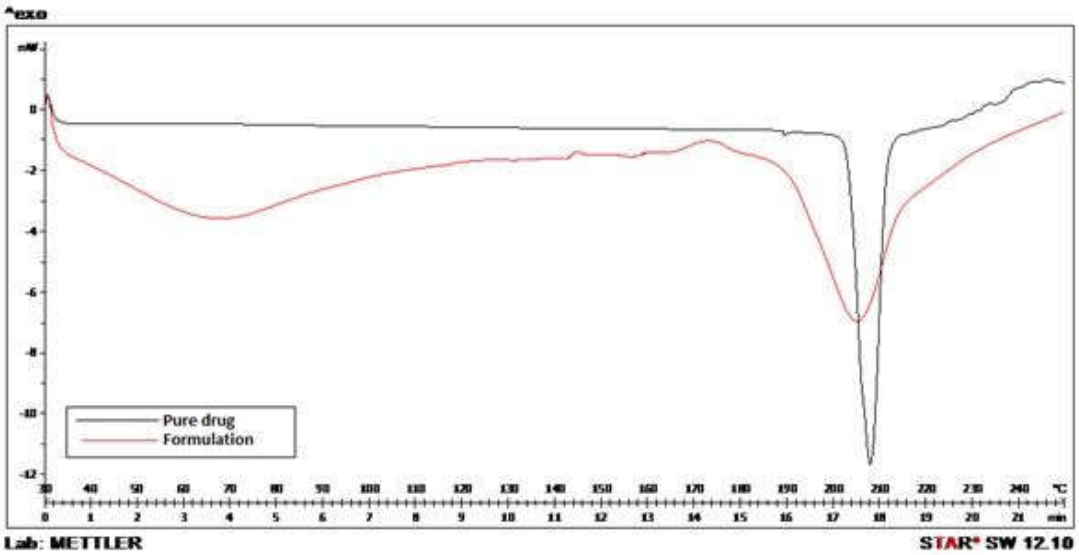
Drug content uniformity

The presence of amlodipine in each tablet was found to be in the rangeof101.01 ±0.05%, indicating its uniformity of distribution among each tablet. It was concluded after comparison with the standard in IP.

DSC study

DSC thermogram of pure amlodipine represented its sharp melting point at 207.40^{0}c (Figure 3) indicating fast transformation with larger enthalpy change (Hadzidedic*et al.,* 2014). Whereas the formulation showed thesame peak with a little decrease in peak intensity confirmed the crystallinity of amlodipine in the formulation. The decreased intensity and less enthalpy change may be due to the presence of MCC 102 in the formulation. No such significant interaction was observed.

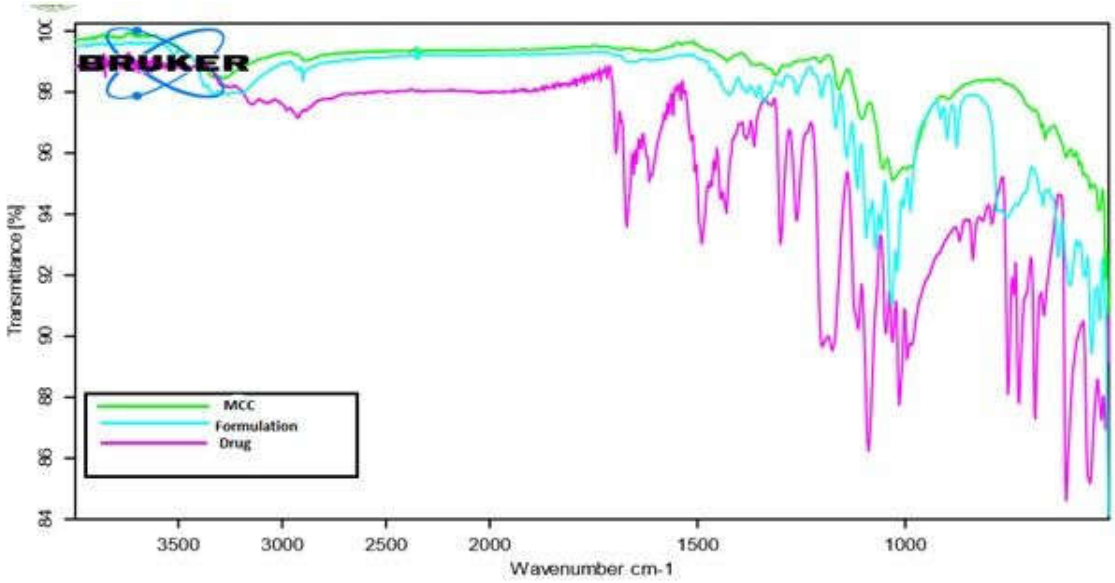
FIGURE 3 - DSC thermogram of pure drug and formulation.



Fourier transform-infrared spectroscopy

The infrared spectrum of pure amlodipine confirmed its functional groups by manifesting its identification bands at 3284 cm^{-1}(asymmetric stretching of NH3), 3077cm^{-1} (asymmetric stretching of CH ring 3), 1666 cm^{-1}(stretching of C-C ring 2 and inplane bending of N10 H), 1611 cm^{-1}(asymmetric bending of NH3) , 1489 cm^{-1}(in plane bending of NH and CH2), 1434 cm^{-1}(asymmetric CH3 bending), 1259 cm^{-1}(NH3 wagging), 1113 cm^{-1} (wagging of C22H3), 1039 cm^{-1}(in plane bending of CH ring 1), 1017 cm^{-1}(in plane bending of CH ring 3), 984 cm^{-1} and 741 cm^{-1} (out of plane bending of CH ring 3 (Mubtasim*et al.,* 2016). Wave no 3600-3200 cm^{-1} and 1780-1650 cm^{-1}were assigned for hydroxyl stretching and the carbonyl stretching vibration in MCC 102 respectively (Figure 4). From the data it was interpreted that there was no significant change in the peaks for the formulated tablet hence the drug and excipient was found to be compatible.

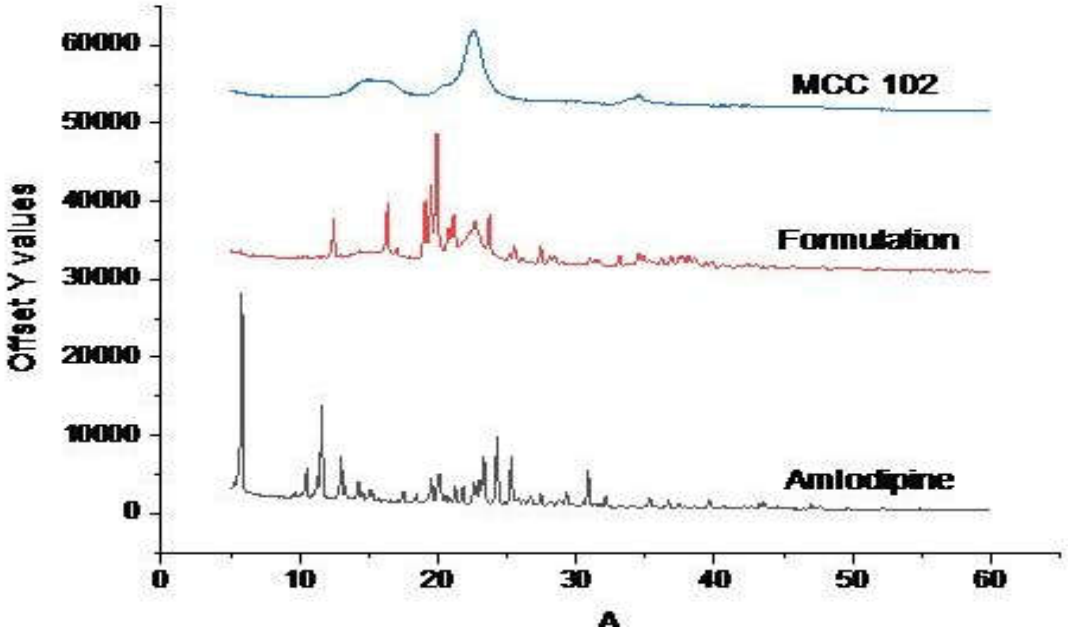
FIGURE 4 - FTIR comparison Study



X-ray diffraction

The diffractogram of pure drug confessed the characteristic peaks at 3.53^0, 10.21^0, 12.86^0, 14.29^0, 21.73^0, 24.03^0, 26.61^0, and 31.82^0 (Kapor*et al.,* 2010). The sharp peaks with high intensity reflected the crystalline nature of amlodipine. A broad amorphous hump and a tiny peak which were more pronounced in MCC 102 were observed at 22.84^0 and 35^0 2Ɵ angle (Figure 5). The characteristic peaks of the formulation did not show any significant difference while comparing with pure amlodipine and MCC 102, which is a reflection of the crystalline nature of amlodipine in the formulation.

FIGURE 5 - XRD study of pure drug, formulation, MCC 102



***Insilico* docking study**

The resulting score of amlodipine-MCC 102 complex was found to be -2.9 k cal/ mol which demonstrated the stable interaction. Detailed predicted interaction between two compounds is listed in table V and elucidated in figure 6.

FIGURE 6 - Docking interaction of amlodipine and MCC 102 (A), bonding relationship along with bond length of the amlodipine and MCC 102 (B)

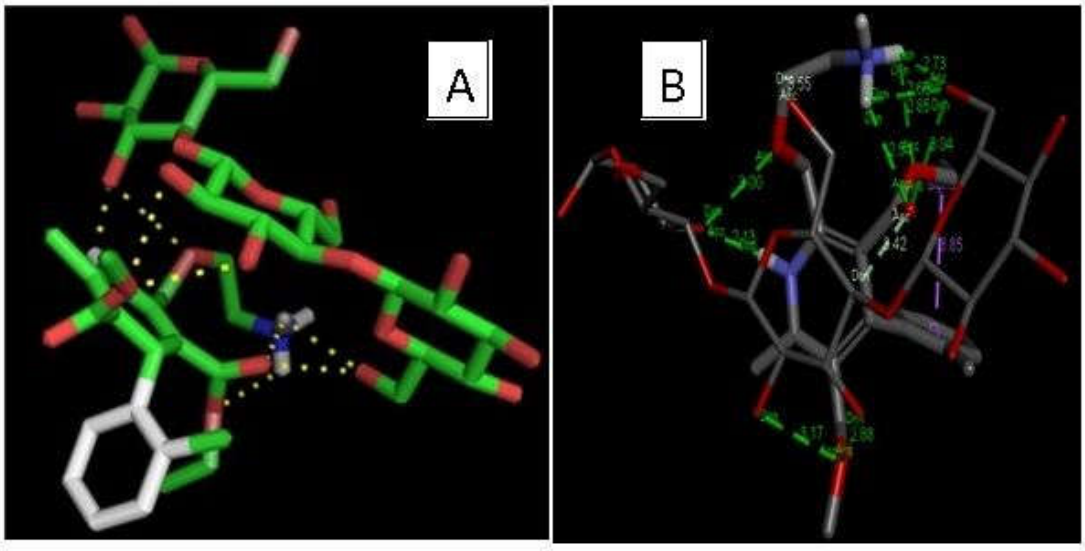
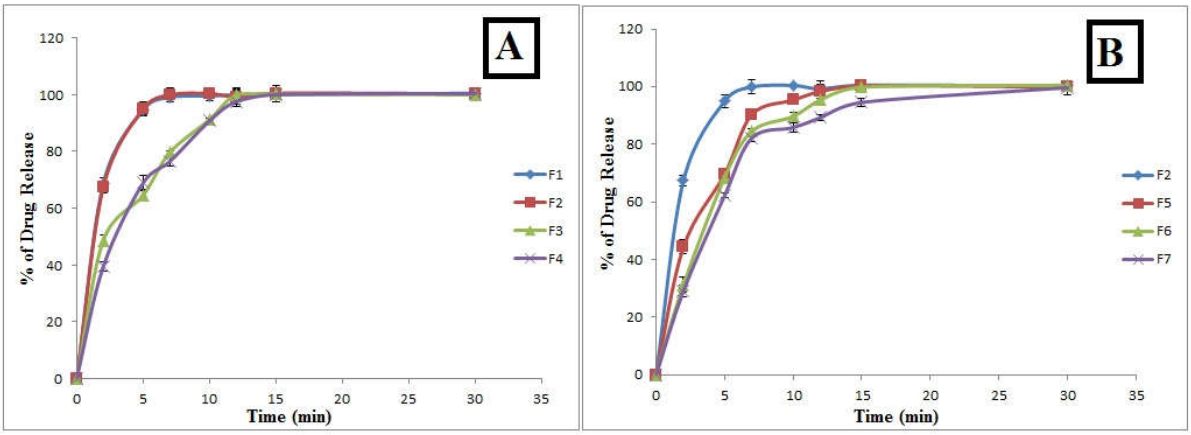


TABLE V - Summary of the predicted interaction by *in silico* docking study

Sl no.	Colour of bond	Types of bond	Bond distance	Angle DHA	Angle HAY	Angle XDA	Angle DAY
1	Green	Conventional hydrogen bond	2.134	132.535	75.491		
2	Green	Conventional hydrogen bond	2.543	129.25	90.413		
3	Green	Conventional hydrogen bond	2.599	100.05	47.523		
4	Green	Conventional hydrogen bond	2.847	105.395	95.821		
5	Green	Conventional hydrogen bond	2.734	92.154	74.02		
6	Green	Conventional hydrogen bond	3.051			18.384	130.353
7	Green	Conventional hydrogen bond	2.876			59.617	106.832
8	Green	Conventional hydrogen bond	3.168			23.734	92.808
9	Green	Conventional hydrogen bond	2.995			23.182	95.122
10		Carbon hydrogen bond	3.554			97.389	37.642
11		Carbon hydrogen bond	3.421			11.465	123.61
12		Pi-sigma bond	3.850				

In-vitro dissolution profile

FIGURE 7 - Comparison release profile of F1 to F4 (MCC 102 variation) (A) and F2, F5, F6 and F7 (pressure variation) (B)



From the Above graph (Figure 7 A) it was determined that the tablet containing 25%MCC 102 and without MCC 102 showed a slow drug release rate compared with the other two formulations, Where the tablet containing 33.33% MCC 102 and 50% MCC 102 showed nearly equal drug release rate up to 100%. So the tablet containing 33.33% MCC 102 was optimized. After variation of pressure to the optimized (33% MCC 102) formulation the comparison graph showed the formulation containing33.33% of MCC 102 and with one Ton pressure reveal better drug release compare with the tablet prepared with 2, 3, and 4 Ton pressure (Figure 7 B).

TABLE VI – Maximum dissolving time (MDT) and dissolution efficiency (DE) of amlodipine immediate release tablets

Formulation code	**% Of drug dissolved (Q%)**	**Dissolution time (DT)**	**Dissolution efficiency**
F1	99.56	10	90.92
F2	100.43	10	90.29
F3	99.93	12	88.74
F4	99.99	15	86.81
F5	98.35	12	88.97
F6	99.87	15	86.82
F7	99.72	30	85.85

Table VI shows a comparison profile of dissolution metrics such as dissolution efficiency (DE) and the quantity of drug dissolved in a given period expressed in percentage (Q %). All the formulations revealed the dissolution efficiency above 85%. In previous articles, high dissolution efficiency was confirmed for immediate release dosage form (Malufet *al.,* 2009). Among all the formulations F1 and F2 had similar dissolution efficiency and took 10 minutes to release 100% of the drug in to the dissolution media. As a result, when the MCC concentration and all the dissolution parameters were correlated, F2 was shown to be the best formulation among all. Figure 8 shows the comparison of dissolution parameters (t25, t50, and t90) for amlodipine immediate release tablet. In case of MCC variant formulations,no significant difference was found between the F1 and F2 formulation. All the pressure varied formulations i.e. F5, F6, and F7 exhibited a more retarded release than F2. As a result, it was confirmed that the formulation with 33.33% MCC and one ton pressure was finest to all.

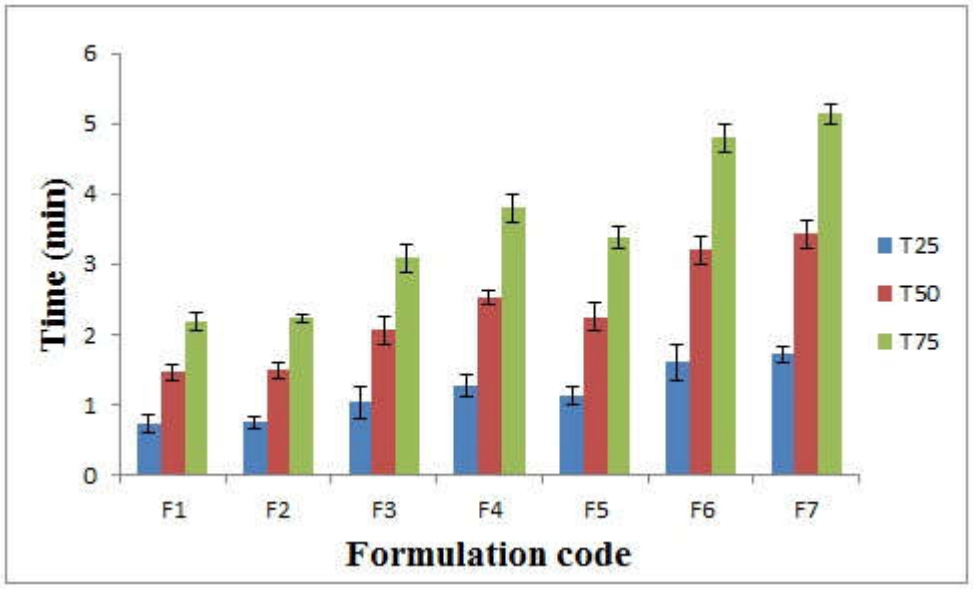


FIGURE 8 - Comparison of dissolution parameters (t25, t50, and t90) for amlodipine immediate release tablet

CONCLUSION

Urgent action is always demanded when it comes to life threatening. Here we prioritize the urgent action by keeping the cost of the formulation in eye to develop an efficient and most situated procedure to meet the objective. CCS and MCC 102 helped in the

betterment of drug release. Factors like MCC 102 concentration with CCS and compaction pressure have shown a spectacular impact on the tablet performance. By compiling all the above data and characterisation outcomes it can be concluded that MCC 102 in 33.33% along with CCS at one ton pressure is the most suitable and efficient process for the development of amlodipine besylate immediate release tablet without hampering the therapeutic efficacy drug. This set of findings could show significant benefits in industrial large scale preparation.

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DECLARATIONS OF INTERESTS

The authors report no conflict of interest to anybody.

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