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Research Article

Formulation, Evaluation and Optimization of Nebivolol Hydrochloride Mouth Dissolving Film

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ABSTRACT

The present study is an effort to enhance solubility and to formulate and optimized BCS class II antihypertensive drug Nebivolol HCl a selective β1 blocker. Solid dispersions with binary and ternary ratios of drug: carrier: surfactant was developed by solvent evaporation method. Results confirmed solid dispersion comprising Nebivolol HCl: Poloxamer: Gelucire in ratio enhanced solubility. FTIR, DSC, PXRD and SEM studies confirms compatibility and polymorphic form of drug converted from crystalline to amorphous due to solid dispersion. Ternary solid dispersion 1:7:9 was best selected ratio for development of mouth dissolving film (MDF) by solvent casting method. Preliminary trial batches of MDF were developed and approved batch showed desirable % drug release and folding endurance was further selected for optimization by 32 full factorial design. Two independent variables selected were HPMC E 15 (X1) and TEC (X2) and two responses as % drug release and folding endurance as Y1 and Y2 respectively. The MDF were evaluated for their physio mechanical parameters like visual inspection, mouth feel, Thickness, weight variation, Dispersion and Disintegration test. The optimized MDF coded as OB using HPMC E 15 225 mg and TEC 0.7 ml was selected as suggested by software with high desirability of 0.787 with drug release of 94.92% within 120 sec. and folding endurance 319. From the above results it can be concluded that solid dispersion technique was effective strategy to enhance solubility of Nebivolol and all evaluation results suggested that MDF with excipients used improved drug release rapidly and it may improve bioavailability.

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Introduction

Numerous researches have been conceded with the aim of discovering an ideal formulation for immediate drug delivery to treat numerous complications in the field of pharmacotherapy. Pharma research focus on improving the oral bioavailability of drug comprises the enhancing solubility, dissolution rate permeability of poorly

water soluble and permeable drugs (Kumar *et.al.* 2011). Low solubility poses a face challenge in preformulation and formulation development stage and is one of key factor to attain desired drug concentration systemically to achieve pharmacological response (Patil *et.al.* 2011). The BCS class II type drugs often require the high doses to achieve therapeutic plasma level after oral administration which may lead to toxicity. Among the five key physicochemical properties in early compound screening like solubility, pKa, permeability, stability and lipophilicity, poor solubility tops list of undesirable compound properties (Khadka *et.al.*2014)

In the process of solubilization improvement various factors like temperature, molecular and particle size, nature of solute and solvent, polymorphs etc plays key role. To improve systemic availability of drug administered orally various approaches may be implemented or alternative may be change in route of administration (Thakkar *et.al.* 2010). Out of this improvement of oral bioavailability of drug is most realistic approach and most preferred and convenient. The techniques or approach can be used like physical modification i.e. solid dispersion, micronization, complexation, modification of crystal habit, polymorphs, self emulsifying drug delivery system etc. Chemical modification i.e. formation of salts and prodrugs, co-solvency, co-crystallization, hydrotrophy etc., Nanotechnology based approaches like nanosponges, nanocrystals, nanosuspensions. (Ramesh *et.al.* 2016)

Solid dispersion is one of the best fitted approach for the solubility enhancement. It is a group of solid products consisting of at least two different components, the hydrophilic matrix and hydrophobic drug (Sahi *et.al.* 2017). The matrix may be crystalline or amorphous; basically amorphous having good solubility than the crystalline, because no energy is required to break up crystal lattice of drug during dissolution process (Shaikh *et.al.* 2016).The solid dispersion technologies are particularly promising for the improving the oral absorption and bioavailability of the BCS Class II drugs. The modified Noyes-Whitney equation gives some idea how dissolution rate of even very poorly soluble compounds are might be improved to the minimize limitations to oral availability (Gaykwad *et.al.* 2014).

The immediate or fast drug delivery system (FDDS) was the advancement that came into the existence in early 70's to counter drawbacks over conventional oral dosage forms by rapidly disintegration & dissolve in saliva without use of water (Prabhu *et.al.* 2014). For many patients like paediatric and geriatric it is difficult to swallow tablets and capsules as prescribed. The difficulty in the swallowing or dysphagia is seen to afflict such patients. To overcome the difficulties, several fast dissolving formulations have been developed and available in the market like oral disintegrating tablets (ODT) or mouth dissolving film or strips (Heer *et.al.* 2013).

The MDFs are most advanced form of the oral solid dosage form due to the more flexibility and comfort because of its unique properties. It improves efficacy of drug by rapid disintegration and dissolution within seconds in mouth after contact with the saliva without chewing and use of water to release medication for oro-mucosal absorption to achieve therapeutic effect (Shaikh *et.al.* 2014). MDFs are useful in patients such as the paediatric, geriatrics, bedridden, emetic, diarrhoea, sudden episode of the allergic attacks, or coughing condition for those who have an active life style (Sharma *et.al.* 2015, Chaurasiya *et.al.* 2016).

Hypertension is one of the major disease global burden, occurring as sinister accompaniment to growing populations and is ever increasing worldwide issue. It requires long term medication or drug therapy to maintain appropriate blood pressure. Although there are many class of antihypertensive drugs for clinical but use of β_1 selective beta blocker have a special role in the management of hypertension considering safety and efficacy (whelten *et.al.* 2002). Nebivolol HCl is a new generation beta blocker with a long receptor half life belongs to BCS class II drugs having low solubility and high permeability. It is available in dosage form of 5 mg and has mean half life of 10 hours. After oral administration of Nebivolol HCl is absorbed from the GIT, its absolute bioavailability is approximately 10-13 %. These pharmacokinetic

parameters suggest that formulation with better bioavailability of Nebivolol HCl can be obtained if its solubility is enhanced (Hilas *et.al.* 2009)

Materials and Methods

Materials

Nebivolol was a kind gift from MicroLabs, Banglore, India. Poloxamer 188 and 407, Gelucire 44/14 was procured on demand as free gift sample from the Alkem Laboratories, Mumbai Pvt. Ltd. (Mumbai, India). Ecocool DT was procured on demand as free gift sample from Idealcures, Mumbai. HPMC E5 and E15, Isopropyl alcohol (IPA) and other chemicals were purchased from Loba Chemicals (Mumbai, India) and are of standard pharmaceutical grade and of standard Pharmacopoeia grade.

Methods

Preparation of solid dispersion by binary and ternary system of Drug: Poloxamer 188 and 407: Gelucire 44/14:

For solubility enhancement of Nebivolol HCl was combined with Poloxamer 188 and Poloxamer 407 as solubilizer respectively as solid dispersion binary mixture at different ratio and evaluated for solubility, drug content, *in vitro* drug release and kinetic study (Leuner *et.al.* 2000, Vasconcelos *et.al.* 2007). Physical characterization was assessed by IR spectroscopy, DSC, XRD and SEM analysis (Yushen *et.al.* 2013).

Results revealed that using Poloxomer 407 in binary solid dispersion 1:7 showed better solubility as compare to physical mixture and Poloxomer 188 dispersion (Karekar *et.al.* 2009). But individually Poloxomer 407 not improved solubility to the extent, hence further Nebivolol HCl: Poloxomer 407 was combined with Gelucire44/14 as ternary system at different ratio and evaluated same as above parameters. For this weighed amount of drug and carrier was dissolved in a solvent thoroughly mixed until solvent was evaporated and solid mass was obtained. This mixture was dried in hot air oven Labin LI-87-D at 40°C. The mass was pulverized and stored in a desicator at room temperature and evaluated. All solid dispersion prepared by same process. Ternary solid dispersion Nebivolol: Poloxamer 407: Gelucire 44/14 with 1:7:9 ratio was selected for further study of development of MDF formulation to release drug in immediate manner (Dugar *et.al.* 2016, Eloy *et.al.* 2014).

Table 1: Formulation of Ternary solid dispersion of Drug: Poloxamer 188: Gelucire44/14 and Drug: Poloxamer 407: Gelucire44/14.

Sr. No.	Batch code	Combination	Ratio of Drug: carrier	Sr. No.	Batch code	Combination	Ratio of Drug: carrier
1	TM1	Nebivolol HCl: Poloxamer 188: Gelucire 44/14	1:8:1	11	TM11	Nebivolol HCl: Poloxamer 407: Gelucire44/14	1:7:1
2	TM2		1:8:2	12	TM12		1:7:2
3	TM3		1:8:3	13	TM13		1:7:3
4	TM4		1:8:4	14	TM14		1:7:4
5	TM5		1:8:5	15	TM15		1:7:5
6	TM6		1:8:6	16	TM16		1:7:6
7	TM7		1:8:7	17	TM17		1:7:7
8	TM8		1:8:8	18	TM18		1:7:8
9	TM9		1:8:9	19	TM19		1:7:9
10	TM10		1:8:10	20	TM20		1:7:10

Selection of Film former and plasticizer:

Two grades of HPMC E 5, HPMC E 15 and sodium alginate film forming polymers were tried to develop film at different concentration. Plasticizer play important role for maintaining the flexibility, which is responsible for the good folding capacity of the film. Hence, trials were carried out using various grades of plasticizer like PEG 400, Triethyl citrate (TEC) at different concentrations. HPMC E15 and TEC were selected as film former and plasticizer respectively to develop MDF on basis of the observations (Kulkarni *et.al.* 2010).

Formulation of Preliminary trial batches of MDF by solvent casting method:

Among all available methods solvent casting was widely used method to get a smooth and thin film hence applied to develop Nebivolol MDF. The aqueous solution was prepared of HPMC E15 in 5ml warm distilled water with continuous stirring at 100 rpm to form a homogenous viscous mixture. This was followed by addition of ternary drug solid dispersion, plasticizer, Crosscarmellose sodium, Tartaric acid, Sucralose, Ecocool DT and color were also mixed and sonicated for 25-30 min. Final film solution was cast on previously lubricated fabricated rectangular glass plate. Film was dried in hot air oven at 40°C for 4 hrs. The film was carefully removed and checked for any imperfection. The films were evaluated for mouth feel, thickness, folding endurance, uniformity of weight and dispersion, disintegration test and assay. Selected batch after evaluation was further subjected for optimization study by using Design of experiment. (Kai *et.al.* 2013)

Table 2: Experimental design: independent and dependent variables and the levels used for factorial design.

Factors (Independent variables)	**Levels**			**Responses (Dependent variables)**
	Low -1	**Medium** 0	**High** +1	
X1=Amount of HPMC-E 15(mg)	175	200	225	% Drug released
X2=Amount of TEC(ml)	0.3	0.5	0.7	Folding endurance

Table 3: Composition of experimental formulations (runs).

Batch code	**X1 (HPMC E15)**	**X2 (TEC)**
F1	175	0.5
F2	175	0.3
F3	175	0.7
F4	200	0.5
F5	200	0.3
F6	200	0.7
F7	225	0.5
F8	225	0.3
F9	225	0.7

Table 4: Experimental formulation as per 3^2 factorial design.

Sr. No	**Ingredients (mg/ml)**	**Batch code**								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Nebivolol HCl	95	95	95	95	95	95	95	95	95
2	HPMC E 15	200	200	200	175	175	175	225	225	225
3	TEC	0.5	0.3	0.7	0.5	0.3	0.7	0.5	0.3	0.7
4	Sucralose	50	50	50	50	50	50	50	50	50
5	Tartaric acid	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8
6	Ecocool DT	45	45	45	45	45	45	45	45	45
7	Croscarmellose sodium	20	20	20	20	20	20	20	20	20
8	Coloring agent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
9	Mannitol	25.7	25.9	25.5	50.7	50.9	50.5	0.7	0.9	0.5

Experimental design

To optimize the selected formulation of preliminary experimental batch, the 32 full factorial design was executed. The independent variables were HPMC E 15 (X1) as film forming polymer and Triethyl citrate (X2) as plasticizer. The dependent variables (responses) Y1= % drug release and Y2= folding endurance (no.). In this design, three levels were evaluated, each at the two factor and experimental batches were performed in 9 possible combinations batches F1- F9. The independent and dependent variables and the used levels are summarized in Table 1 and the resulting formulations are listed in Table 2. (Gangurde *et.al.* 2013)

Characterization of Solid dispersion and Nebivolol HCl MDF

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is a useful analytical technique in the confirmation of functional groups. Nebivolol HCl, Poloxamer 188 and 407, Gelucire 44/14 (10 mg) combinations prepared and analysed by ATR JASCO 4000 scanned in the range 4000-400 cm-1 and spectra was recorded. By interpretation of spectra and comparing with reported data, the confirmation of drug and interaction if any was studied.

Differential Scanning Calorimetry (DSC)

The possibility of any interaction between the Nebivolol HCl and Poloxamer 188, 407 and Gelucire44/14 were assessed by carrying out thermal analysis using Shimadzu DSC-60. The weighed amount of sample was first cooled to -10°C and was hold at that temperature for 1 min. The sample was then heated to 250°C at a rate of 10°C/min.

Powder X-ray diffraction (PXRD):

To determine the powder characteristics by using XRD of Nebivolol HCl, Poloxamer 188, 407, Gelucire 44/14 was assessed by Jeon AXD D8 advance. The samples were exposed to Cu Kα radiation under 40 kV and 35mA over the 2θ range from 3° to 70°C at increments of 29.1/s. The obtained diffractrogram were finally interpreted.

Scanning Electron Microscopy

The surface morphology of optimized formulation studied using SEM images. A SEM sample holder with double sided taps and coated with layer of gold of 150˚A for 2 min using sputter coater in vaccum of 3×10-1atm of arogan gas. The samples of solid dispersion, placebo and drug loaded MDFs were examined.

Mouth feel

The formulations were subjected for mouth feel. The placebo MDF was given to volunteers for tasting. As the drug is bitter in taste by adding Sucralose and Ecocool DT was used as diluents, sweetener and masking the better taste (Dahiya *et.al.* 2009).

Thickness

The thickness of film is calculated by using digital Vernier caliper Mitutoyo, Japan at different points of film i.e. four corners and centre. Randomly selected 5 films were selected for thickness measurement with not less than 5 % deviation.

Folding endurance

Folding endurance test was performed by repeated folding the strip at a same point till the film breaks. The number of times strip is folded without breaking is a computed as the folding endurance value. (Pathare *et.al.* 2013).

Uniformity of weight

The uniformity of weight test was performed on randomly selected 10 films and each film weighed separately. After average weight and standard deviation was calculated.

Uniformity of Dispersion

Place 2 film in 100 ml of SSF and stir gently until completely dispersed. A smooth dispersion is obtained which then passed through a sieve with a nominal mesh aperture of 710µm (sieve number 22). No particle must retain on the surface of the sieve is observed.

Assay

The acceptance value of the test is less than 15% in accordance with Japanese pharmacopoeia. According to USP27, the contents should range from 85% to 115% with the standard deviation of less than or equal to 6%. The MDF was placed in conical flask containing 100 ml of SSF pH 6.8.the flask were shaken for 5 minutes. All samples were filtered and analyzed against blank SSF at 281 nm by using UV-Visible spectrophotometer.

Disintegration Test

Official guidelines are not available for MDF dosage form. The disintegration time limits 30 sec or less as compare to orally disintegrating film. Test was performed in 100 ml beaker containing 15 ml SSF pH 6.8 of 37°C temperature. When film was placed in beaker and shaked slightly and time was noted at which film broke or start dissolving.

***In vitro* drug release study**

Dissolution medium to study of mouth dissolving film is used as 15ml of SSF pH 6.8 in 1000 ml beaker. Temperature of dissolution medium was maintained at 37 ± 0.5ºC. Samples were withdrawn at every 10 sec, and replaced with fresh medium as of withdrawn sample. Absorbance of sample is measured against blank SSF pH 6.8 in UV spectrophotometer and the graph was plotted cumulative % drug release Vs time.

Kinetic study

The *In vitro* drug release data were fitted to various release kinetic models viz. first-order, Higuchi, Hixson-Crowell cube root, Korsemeyer-pappas and zero-order (Patel *et.al.* 2012, Verma *et.al.* 2011).

Result and Discussion

Drug polymer physical compatibility and preliminary studies FTIR, DSC, XRD confirmed there was no any interaction and found to be compatible with each other. The binary solid dispersion of drug and Poloxamer 188 with 1:8 ratio and Poloxamer 407 of 1:7 showed significant solubility when no more solubility increases in further combinations hence above combinations were further selected for Ternary system. After various evaluation parameters ternary solid dispersion of Drug: Poloxamer 188: Gelucire 44/14 (1:8:10) ratio showed highest solubility i.e. 56.65 µg/ml, and Drug: Poloxamer 407: Gelucire 44/14 (1:7:9) ratio showed highest solubility i.e.62.79 µg/ml, compared to that of Nebivolol HCl (solubility 0.039µg/ml). Hence Ternary solid dispersion 1:7:9 was selected as best ratio for further development of Mouth dissolving film as a drug.

Table 5: Solubility and drug content of Ternary solid dispersion of Drug: Poloxamer 188: Gelucire 44/14 and Drug: Poloxamer 407: Gelucire 44/14.

Sr. No.	Code	Solubility (µg/ml)	Drug content %	Sr. No.	Code	Solubility (µg/ml)	% Drug Content
1	TM1	38.09	78.2	11	TM11	52.01	85.8
2	TM2	39.72	80.8	12	TM12	52.79	86.4
3	TM3	42.75	82.2	13	TM13	54.10	87.4
4	TM4	45.89	83.4	14	TM14	56.07	87.9
5	TM5	47.55	84.8	15	TM15	56.19	88.2
6	TM6	52.42	86.2	16	TM16	58.78	89
7	TM7	53.12	89.8	17	TM17	59.83	92.1
8	TM8	53.91	91.6	18	TM18	60.01	93.6
9	TM9	55.85	92	19	TM19	62.61	94.2
10	TM10	56.65	92.4	20	TM20	62.79	94.6

Further five different concentrations of HPMC E15, HPMC E 5 and Sodium alginate as film former polymer were tested in the preliminary trial batches. HPMC E 15 200 mg as compared with other polymers formed good film with good folding endurance and was easily peelable selected for further study. Polyethylene glycol 400 and TEC as plasticizer at different concentration were also tested in trails. The film containing 0.5 ml of TEC showed good folding endurance and no oiliness hence selected for optimization and development of MDF.

Characterization of Solid dispersion and Nebivolol MDF

Fourier Transform Infrared Spectroscopy

There is no significant shift observed in a position of featured peaks of Nebivolol HCl as well as Poloxamer 188, Poloxamer 407, Gelucire 44/14. Hence, it can be considered that drug and

polymers are chemically compatible and can be together incorporated in the formulation.

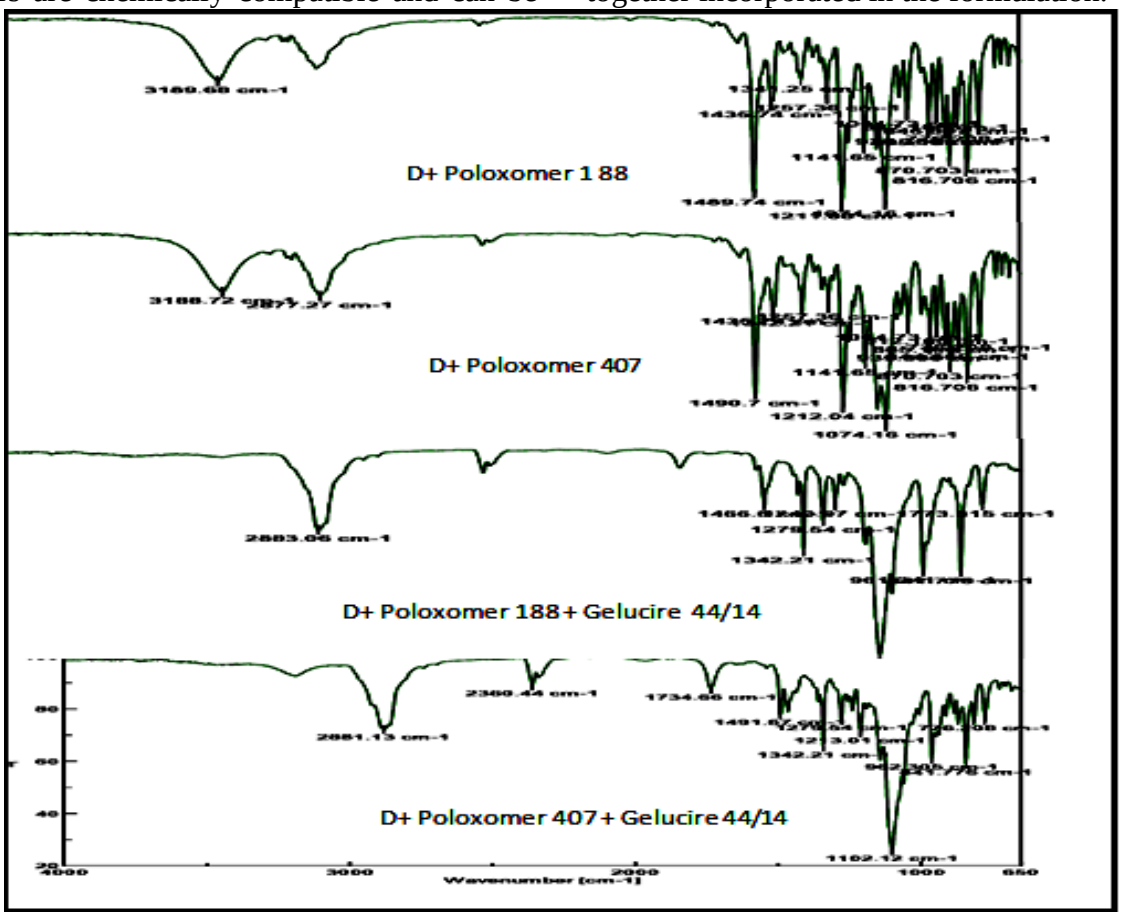

Fig. 1: IR spectra of Nebivolol HCl and polymer combined solid dispersion.

Differential Scanning Calorimetry

In DSC thermo gram of NEB HCl, a sharp endothermic peak is observed at 231.655°C analogues to its melting point. Whereas in thermo graph of solid dispersion a peak corresponding to NEB HCl is absent. This suggests that a complete solution of NEB HCl has formed within the Poloxamer 407 and conversion of physicals state of NEB HCl form crystalline to amorphous.

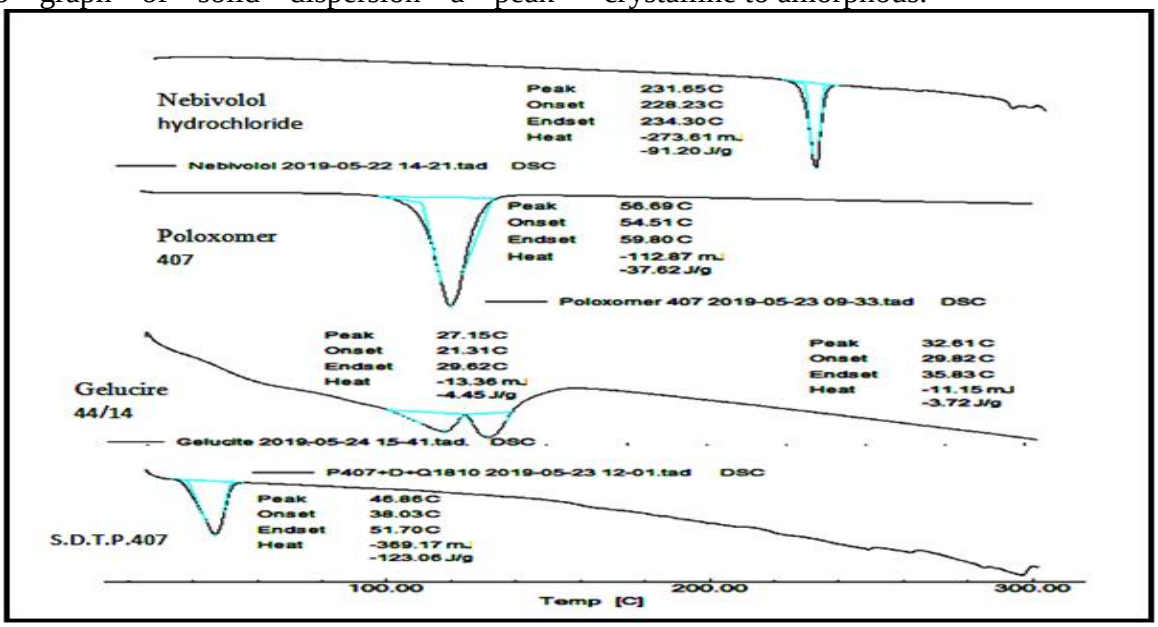

Fig. 2: DSC Thermogram of Drug, polymers and ternary solid dispersion (1:7:9)

Powder X-ray Diffraction

The XRD pattern of solid dispersion in **Figure 3** shows absence of characteristic peaks of Nebivolol HCl in the solid dispersion suggests that complete amorphous nature of drug has taken place. Owing to amorphous structure of dru solubility and hence dissolution of solid dispersion was greatly increased.

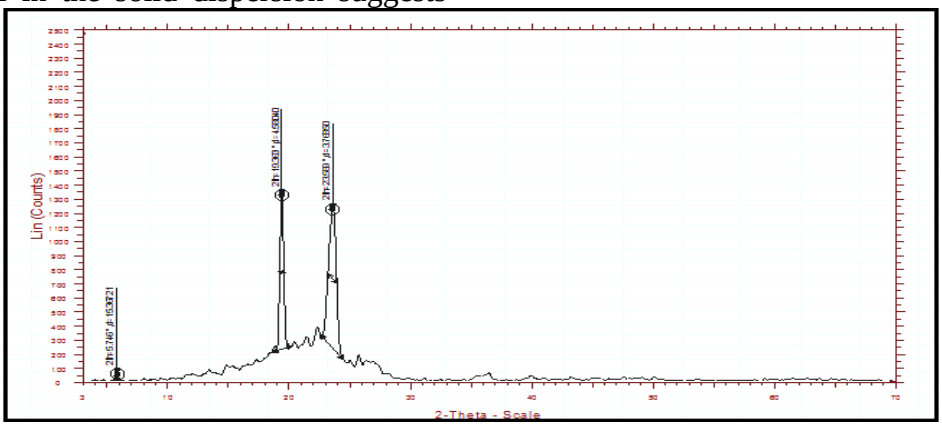

Fig. 3: PXRD of ternary solid dispersion (1:7:9)

Scanning Electron Microscopy

The results obtained revels the fact of formation of more porous particles and the reduction of particle size as compare to drug showed in Figure 4. The micrographs appeared in Figure 5 shows highly porous nature of prepared MDFs. The highly porous nature of films explains the rapid penetration of water, which results in rapid wetting, disintegration, and dissolution in oral cavity.

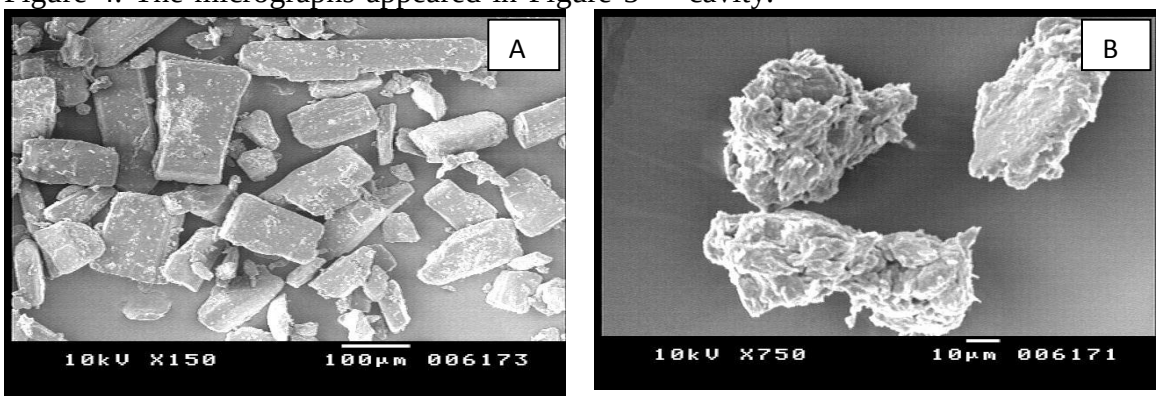

Fig. 4: SEM of (A) Drug and (B) Ternary solid dispersion (1:7:9).

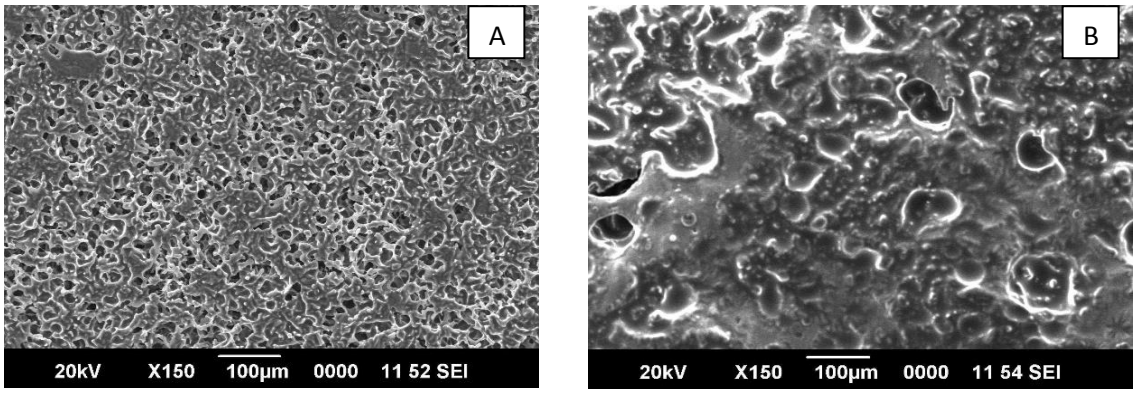

Fig. 5: SEM of placebo MDF's (A) and drug loaded MDF (B)

Optimization of Nebivolol MDF

Visual inspection confirms thin and uniform film and patient acceptance as important factor for the administration of MDF was found to be satisfactory and no oiliness was seen on film. The MDFs were subjected for mouth feel where

volunteers felt good taste in all the formulations. Thicknesses of formulated films were found to be in range 0.040 to 0.064 ±0.004 mm. The mean values are tabulated in Table 6 indicating that as concentration of polymer increases thickness also gradually increases. Whereas, F1 and F5 batches showed least thickness than the other formulations. All the films passed Uniformity of weight values are within standard limit i.e.515.6 to 644±2.16 mg. Results of all the formulation is shown in Table 6. Folding endurance of all batches ranges from 297 to 318 ± 7.5. The result indicates increase in plasticizer concentration increases folding endurance. The average folding endurance of all batches shown in Table 6. Rapid dispersion within several seconds was observed and all particles passed from sieve no. 22 for all batches. The dispersion data is tabulated in the Table 6. Disintegration time of F1-F9 was observed between 28-34 sec. Results obtained indicates increasing polymer concentration increases disintegration time. Assay result indicated that all MDF batches drug content was uniform. The ranges of drug content in all the batches were observed between 62.4 to 73.7± 0.09 shown in Table 6.

Table 6: Evaluation of MDF formulation F1-F9 batches

Code	Mouth feel	Thickness (mm)	Uniformity of weight	Folding endurance	D.T. (sec)	% Drug content
F1	+	0.040 ± 0.004	629.3± 5.7	302±2.1	30±0.4	64.9 ± 0.24
F2	+	0.064 ± 0.002	619 ±4.4	297±2.4	31±0.8	69.2 ± 0.12
F3	+	0.056± 0.002	615 ±3.77	317±4.4	32±0.9	64.9 ± 0.29
F4	+	0.053 ± 0.004	591 ±2.44	294±10.0	28±0.4	50.3 ± 0.08
F5	++	0.045± 0.004	517 ±6.16	301±6.9	30±0.5	66.8 ± 0.20
F6	+	0.054± 0.005	515.6 ±5.73	305±8.2	30±1.4	72.8 ± 0.16
F7	++	0.056± 0.009	642± 1.63	298±12.2	35±1.2	73.7 ± 0.09
F8	+	0.052± 0.002	642.6 ±1.24	318±7.5	34±1.6	62.4 ± 0.04
F9	+	0.051± 0.004	644 ±2.16	315±5.3	33±1.4	65.4 ± 0.12

*No bitter taste +, Slight bitter taste ++, Strong bitter taste +++

***In vitro* drug release study**

The cumulative drug release was calculated on the basis of drug content present in respective film. The result obtained for all batches F1-F9 is shown in Figure **7.** The rapid drug dissolution at the end of 120 sec. observed in most of batches but F5 batch shows the highest release than other formulations. Slow release was observed in F3 with release 63.82% at the end of 120 sec. due to increase in polymer concentration. The increase concentration of a polymer results in a formation of strong matrix layer and caused more intimate contact between particles in the swollen matrices, leads to decrease in the drug release.

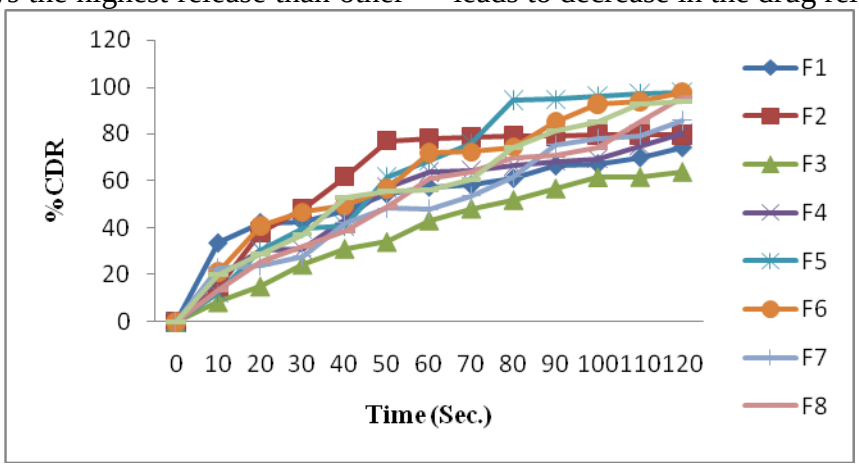

Fig. 7: % CDR Vs Time Plot of Nebivolol MDFs (F1-F9).

Drug release kinetics

Dissolution kinetics for films was analyzed and Higuchi order kinetic equation are found to be good fit for release profiles, with the R^2 values close to the unity. The mouth dissolving films follow the zero order release profile and same

amount of the drug by unit of time and release of drug from formulation occurs due to the swelling and erosion of the polymer. The results obtained are shown in **Table 7.**

Table 7: Drug Release Kinetics Study of Nebivolol MDFs (F1-F9).

Sr. No.	Formulation batches	Zero order	First order	Higuchi order	Hixon-Crowell	Korsmeyer-Peppas
1	F1	0.8099	0.9387	0.9616	0.8848	0.8615
2	F2	0.7253	0.7979	0.889	0.7668	0.9347
3	F3	0.9665	0.9918	0.9674	0.9833	0.9951
4	F4	0.8948	0.9636	0.9711	0.9381	0.9503
5	F5	0.9353	0.9351	0.9508	0.9646	0.8125
6	F6	0.9356	0.9104	0.9855	0.979	0.9449
7	F7	0.9588	0.9511	0.9547	0.9766	0.9513
8	F8	0.971	0.8565	0.9652	0.9671	0.9848
9	F9	0.96	0.9249	0.9748	0.9792	0.9615

Optimization

The 3^2 factorial experimental designs were selected and as per required 9 batches were prepared. The ranges of the % drug released (Y1) and folding endurance (Y2) are 74.32-97.8% and 294-318 respectively. The all responses observed for a 9 formulations prepared were simultaneously fitted to the linear, 2FI, quadratic and cubic models by using Design Expert® software version 11.1.2.Stat-Ease Inc. It was observed that best-fitted model were quadratic and linear for the folding endurance and the %drug release respectively. It was evident two independent variables, namely the concentration of HPMC E15 (A), and concentration of TEC (B), respectively have the interactive effects on the two responses, Y1 and Y2. The model proposes the following polynomial equation for % drug release % drug released = 67.26- 0.0500 A – 2.91 B– 0.5075 AB + 19.25 A^2 + 7.96 B^2. The model proposes the following polynomial equation for folding endurance Folding endurance = 305.22 + 5.17 A + 2.17 B.

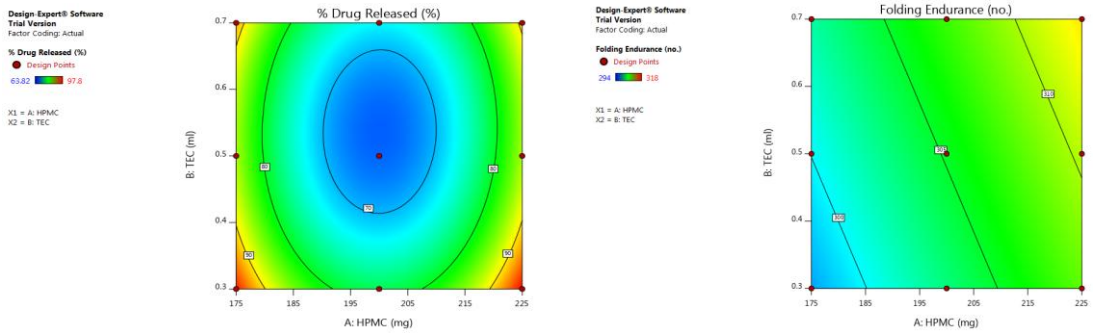

Fig. 7: 2D Contour plot of % drug release and folding endurance

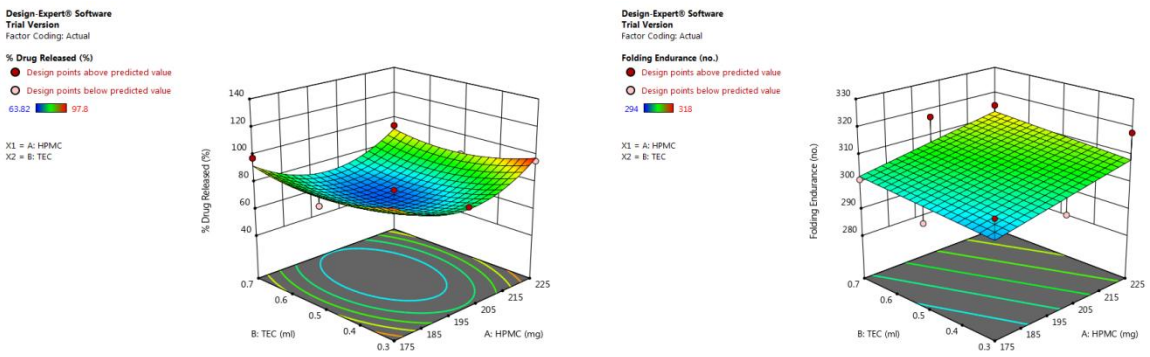

Fig. 8: 3D Surface plot of % drug release and folding endurance.

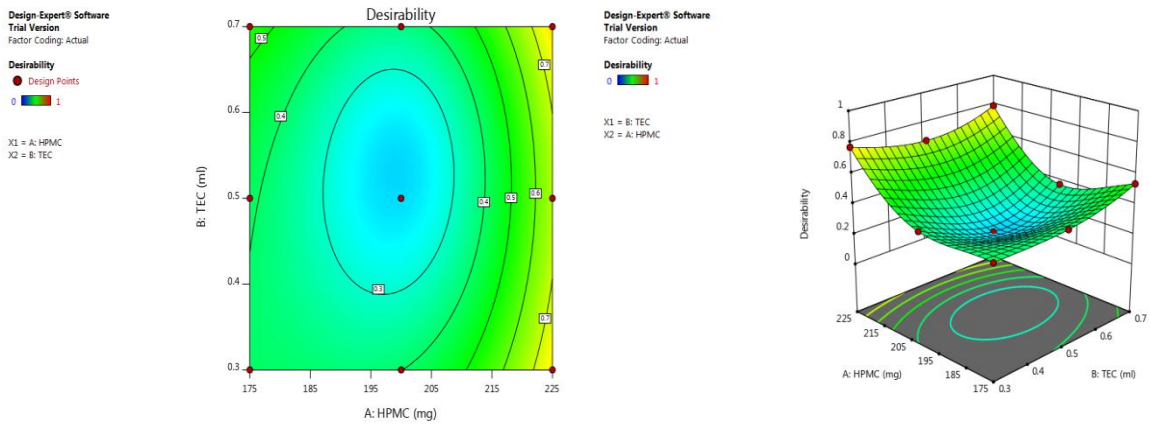

Fig. 9: 2D Contour and 3D Surface plot of Desirability

After the analysis of a both independent and dependent variables the Design Expert® software gave almost 11 solutions with the various desirability but the only one batch was selected with desirability near to the one. The solution formulation batch (OB) with high desirability of 0.787 selected, having concentration of HPMC E15 polymer (225 mg) and concentration of TEC (0.7ml). It can be concluded that the equations are describe adequately influence of selected independent variables on responses under study. It indicates that optimization technique was appropriate for the optimizing the MDFs formulation. Therefore it can be said that the fast release of drug occurs from the film at a lower concentration of plasticizer and the higher concentration of the polymer. It was found that the enhancing the polymer concentration shows the negative effect on a folding endurance and drug release. But when concentration of the TEC was increased, it had positive effect on folding endurance and drug release.

Evaluation for optimize formulation

The optimized batch (OB) was having composition containing HPMC E15 which show good desired release pattern and TEC shows good folding endurance. The optimized batch provide desired values for percentage drug released of 94.92 % in 120 sec and folding endurance was 319± 5.3 with thin layer of 0.052 ± 0.004 mm. Results obtained are shown in below Table 8 and Figure 10 and 11 shows the actual film produced and *In vitro* dissolution data of optimized formulation respectively.

Table 8: Evaluation of Formulation (OB)

Sr. No.	Evaluation parameter	Results
1	Visual Inspection	oiliness was not observed
2	Mouth Feel	+
3	Thickness	0.052 ± 0.004
4	Weight variation	648 ± 2.16
5	Folding endurance	319± 5.3
6	Dispersion test	No particle of MDF retain on Sieve No. 22
7	Disintegration test	32 ± 1.4
8	% Drug content	65.7 ± 0.12
9	*In vitro* drug release	94.92 ± 0.01

± indicates S.D; n=3

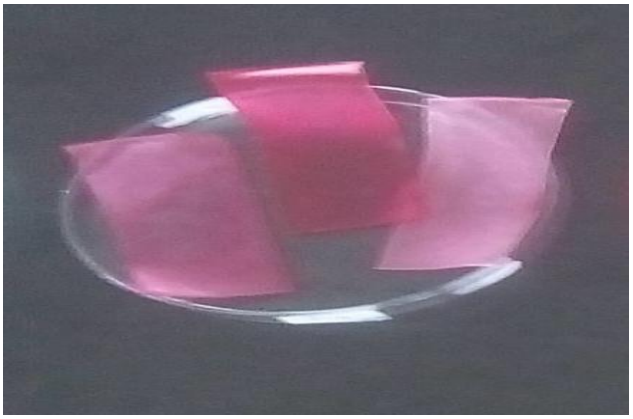

Fig. 10: Film of Final Optimized Batch (OB)

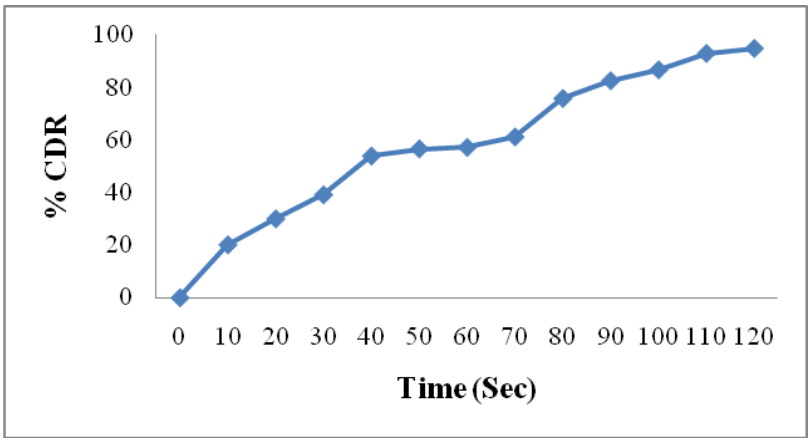

Fig. 11: *In vitro* drug release of Optimized batch (OB)

Conclusion

The present study concludes that when Nebivolol HCl, Poloxamer 407 and Gelucire 44/14 combined together in form of ternary solid dispersion helps to improve the drug solubility by 64 folds at ratio of 1:7:9 respectively. Further to achieve immediate release the Nebivolol HCL MDFs were prepared using different film formers and plasticizers tested among all HPMC E15 and TEC showed satisfactory drug release within time and acceptable physico mechanical characteristics. Through design of experiment optimized formulation batch suggested and formulated with HPMC E15 225 mg and TEC 0.7 ml showed rapid drug release with good folding endurance and with good mouth feel. Thus, the designed formulation can be considered as one of the promising formulation technique to achieve immediate drug delivery for emergency conditions.

Conflict of Interest

There are no conflicts of interest.

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