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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF DILTIAZEM HYDROCHLORIDE BY MELT GRANULATION TECHNOLOGY

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ABSTRACT
The objective behind present study was to formulate and evaluate sustained release tablet of Diltiazem hydrochloride by using different polymers by melt granulation technology and to study the effect of various concentrations of polymers on release rate from tablet. Tablets were prepared using bees wax, carnauba wax, paraffin wax as release ratardent polymers. The drug and excipient compatibility study was done by FTIR method using KBr pellet method. The granules prepared by melt granulation technique evaluated for characterization such as bulk density, tapped density, hausners ratio, angle of repose, cars index all granules shows good flow property. The tablet of Diltiazem HCL evaluated for characterization such as hardness, friability, weight variation and content uniformity all tablets shows sufficient hardness and friability shows that tablets are having sufficient strength. All results were satisfactory. The *in vitro* drug release studies for the prepared formulation were conducted for a period of 12 h using an EDT 08LX dissolution tester USP Type - II apparatus (rotating paddle) set at 100 rpm and a temperature of 37 ± 0.5°C formulation was placed in the 900 ml of the medium. For first 2 h tablet was placed in 1.2 pH acidic medium which was replaced with 7.4 pH phosphate buffer for remaining 10 h. From the dissolution study and comparative graph it was concluded that increase in concentration of wax shows decrease in drug release from tablet. Batch F3 shows 99.84 % drug release at 12 h. *In vitro* release data of optimized formulations (Batch F3) was fitted to various kinetic models like zero order, first order, Higuchi, korsmeyer-peppas and pass Higuchi model as it has highest r^2 value (0.955) among all models.
Keywords: Diltiazem hydrochloride, Bees wax, Carnauba wax, Paraffin wax, Melt granulation.

INTRODUCTION

Oral sustained release systems continue to dominate the market despite the advancements made in other drug delivery systems in order to increase the clinical efficacy and patient compliance. From a practical pharmaceutical view point, numerous types of polymers are currently employed to control the drug release from the pharmaceutical dosage form. Oral sustained release systems are mainly grouped into three types, e.g. reservoir, monolithic and matrix types[1, 2]. Diltiazem is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half life (3-5 h), high aqueous solubility and frequent administration (usually three to four times a day) make it a potential candidate for sustained release preparations[3, 4]. Hydrophobic wax matrix system is being widely used in oral sustained drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Natural waxes have been investigated for sustained release of highly water soluble drugs[5]. Hydrophobic wax matrix system is being widely used in oral sustained drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Natural waxes have been investigated for sustained release of highly water soluble drugs[3]. These materials are readily available and expected to be relatively inexpensive, biocompatible, biodegradable and ecofriendly. Carnauba wax, due to its ease and safety of application, drug embedding ability and chemical inertness has also been used as rate retarding polymer and extensively studied by different investigators[6, 7].

MATERIAL AND METHODS

Diltiazem Hydrochloride is procured from Sun pharmaceutical Ltd, Mumbai, India. Carnauba wax, Bees wax, Paraffine waxes were procured from Colorcon Asia Pvt Ltd., Mumbai, India. Talc, Lactose Monohydrate and Magnesium Stearate were procured from S.D. Fine chemicals Ltd., Mumbai, India. All reagents and chemicals used were of analytical grade.

Preparation of Diltiazem Hydrochloride Sustained Release Tablet

The meltable binder Carnauba wax, Paraffine wax and Bees wax were separately melted in porcelain dishes on a water bath maintained at constant temperature as per their melting points. Diltiazem HCl and Lactose Monohydrate was gradually added to the molten wax with continuous stirring in all porcelain dishes, the molten mixture was allowed to cool and solidified at room temperature. The drug was present in its solid form within the molten mass. The solidified mass was pulverized in mortar and sieved through a 16 # screen.[8] then the granules were compressed in tablet form using 7 mm punch. The tablets were prepared by melt granulation using different concentrations of waxes such as 30 %, 40 %, 45 %. w/w. Batch F1, F2, F3 contain 35 %, 40 %, 45 % w/w carnauba wax respectively and Batch F4, F5, F6 contain 35 %, 40 %, 45 % w/w paraffin wax respectively and Batch F7, F8, F9 contain 35 %, 40 %, 45 % bees wax respectively. In all formulations concentration of Diltiazem HCl was 36 % w/w. (Table 1)

Evaluation

Pre compression parameters

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder

cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone respectively.[9]

Bulk Density

Apparent bulk density was determined by pouring pre- sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$Db = M / V0$$

Where, M is the mass of powder and V0 is the Bulk volume of the powder.

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder and Vt is the tapped volume of the powder

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [TBD-LBD] / TBD \times 100$$

Hausner's Ratio

Calculated by the formula;

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk density}$$

Post Compression Parameters

Physical Appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odor, taste, surface texture and consistency of any identification marks.

Hardness Test

Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. The resistance of tablets to breakage under conditions of storage, transportation or handling before usage depends on its hardness. The hardness of tablet of each formulation was checked by using Monsanto Hardness tester in terms of kg/cm^2

Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier caliper. It was determined by checking ten tablets from each formulation

Friability Test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 10 tablets is taken and these are placed in the Friabilator, rotating at 25 rpm for 4 minutes. The difference in the weight is noted and expressed as percentage. It should be preferably below 1.0 %.

$$\text{\% Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test, W_2 = weight of tablets after test

Weight Variation

20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.[10]

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

Uniformity of Drug Content

Ten tablets from each formulation were powdered. The powdered sample equivalent to 72 mg of drug was transferred to a 100 ml volumetric flask. Required amount of media was added, mixed and filtered; the filtrate was suitably diluted with media and analyzed against blank by UV spectrophotometer at 236 nm for model drug, (Shimadzu UV-1800)[11]

Dissolution Studies

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation to release percentage of drug under specified conditions.

Analysis of Release Data

The release data obtained were treated according to zero order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models.

Table 1: Composition of All Batches (Quantity In mg/tablet)

Batch	Diltiazem Hcl	Carnauba Wax	Paraffine Wax	Bees Wax	Lactose	Talc	Mg. Stearate	Total Wt
F1	72	70	----	----	54	2	2	200
F2	72	80	----	----	44	2	2	200
F3	72	90	----	----	34	2	2	200
F4	72	----	70	----	54	2	2	200
F5	72	----	80	----	44	2	2	200
F6	72	----	90	----	34	2	2	200
F7	72	----	----	70	54	2	2	200
F8	72	----	----	80	44	2	2	200
F9	72	----	----	90	34	2	2	200

Table 2: Characterization of Granules of Sustained Release Formulations of Different Batches

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (CI) (%)	Hausner's ratio (HR)	Angle of repose (θ)
F1	0.555 ± 0.001	0.642 ± 0.002	13.28 ± 0.21	1.15 ± 0.02	27.45 ± 0.65
F2	0.570 ± 0.001	0.654 ± 0.003	12.84 ± 0.25	1.14 ± 0.03	27.40 ± 0.70
F3	0.695 ± 0.002	0.793 ± 0.002	12.35 ± 0.24	1.14 ± 0.01	27.00 ± 0.78
F4	0.615 ± 0.003	0.725 ± 0.001	15.17 ± 0.54	1.17 ± 0.04	28.59 ± 0.84
F5	0.690 ± 0.001	0.794 ± 0.003	13.09 ± 0.45	1.15 ± 0.02	28.52 ± 0.95
F6	0.720 ± 0.010	0.820 ± 0.001	12.19 ± 0.84	1.13 ± 0.04	28.01 ± 0.99
F7	0.585 ± 0.002	0.695 ± 0.002	15.82 ± 0.45	1.18 ± 0.03	29.59 ± 0.62
F8	0.665 ± 0.010	0.781 ± 0.001	14.85 ± 0.65	1.17 ± 0.05	29.48 ± 1.01
F9	0.710 ± 0.001	0.820 ± 0.003	13.41 ± 0.55	1.15 ± 0.04	29.10 ± 1.20

Table 3: Physical Characterization of Tablets

Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	200.85 ± 2.30	3.21 ± 0.08	5.4 ± 0.22	0.35 ± 0.06	98.98 ± 2.01
F2	201.44 ± 1.90	3.15 ± 0.09	5.6 ± 0.23	0.32 ± 0.05	98.76 ± 1.21
F3	203.24 ± 1.85	3.25 ± 0.07	5.7 ± 0.21	0.30 ± 0.05	100.00 ± 2.21
F4	202.31 ± 1.54	3.24 ± 0.06	5.1 ± 0.22	0.45 ± 0.06	99.83 ± 3.01
F5	200.10 ± 1.78	3.21 ± 0.05	5.2 ± 0.24	0.40 ± 0.07	98.88 ± 2.14
F6	199.90 ± 2.41	3.22 ± 0.05	5.4 ± 0.22	0.32 ± 0.05	100.10 ± 1.54
F7	199.58 ± 2.65	3.24 ± 0.06	5.2 ± 0.24	0.55 ± 0.08	99.98 ± 2.47
F8	201.42 ± 2.10	3.21 ± 0.05	5.3 ± 0.23	0.50 ± 0.03	99.13 ± 2.14
F9	203.20 ± 1.96	3.25 ± 0.07	5.5 ± 0.21	0.45 ± 0.04	101.00 ± 1.10

Table 4: *In-vitro* Drug Release Profile

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	5.30	6.96	6.46	5.30	6.63	5.80	5.80	2.48	2.65
1	11.30	13.30	14.21	15.21	15.21	13.62	12.21	9.21	6.97
2	30.14	25.54	25.24	33.21	27.36	23.15	30.25	23.24	18.32
3	44.24	40.12	37.25	54.25	42.36	38.25	48.36	40.25	32.52
4	60.45	54.21	50.41	73.21	52.36	48.58	65.35	52.21	45.24
5	71.21	62.24	60.21	88.25	66.58	58.36	78.36	65.32	60.52
6	80.21	71.25	68.21	95.21	78.32	70.56	89.32	78.25	74.25
7	90.14	80.21	76.25	99.44	89.54	80.25	96.25	89.32	85.36
8	95.54	87.25	83.54		96.25	90.24	99.33	95.35	92.35
9	99.40	94.51	90.21		99.00	96.35		99.18	96.53
10		97.24	95.52			99.23			99.24
11		99.44	98.21						
12			99.84						

Table 5: Evaluation of Drug Release Kinetics

Batch no.	R^2 values (Correlation coefficient)				
	Zero order	First order	Higuchi	Korsmeyer- Peppas	
				R^2 value	n value
F3	0.944	0.906	0.955	0.747	1.279

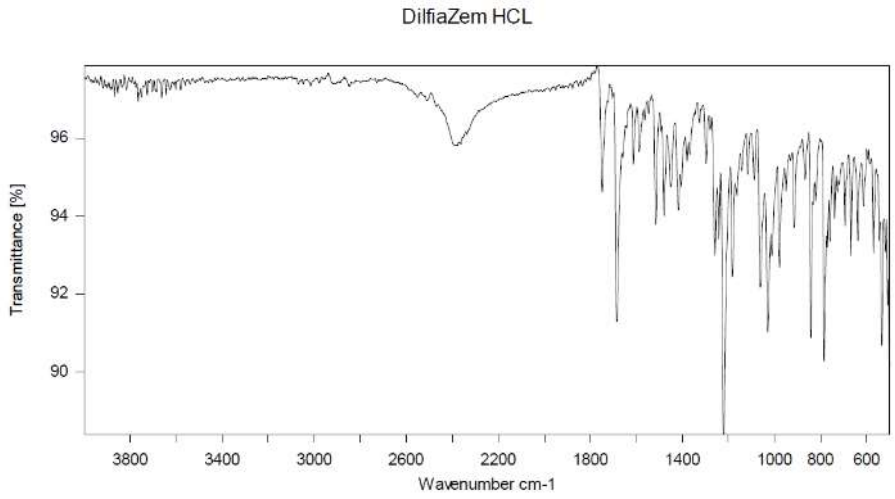


Figure 1: FTIR Spectrum of Diltiazem HCL

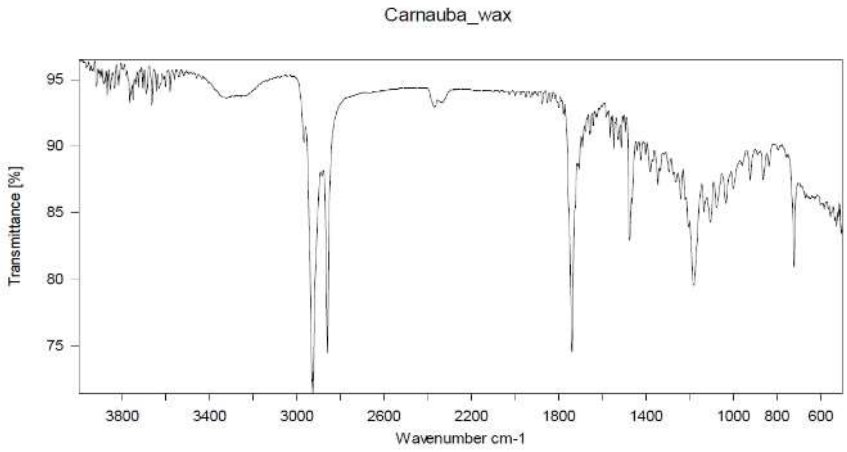


Figure 2: FTIR Spectrum of Carnauba Wax

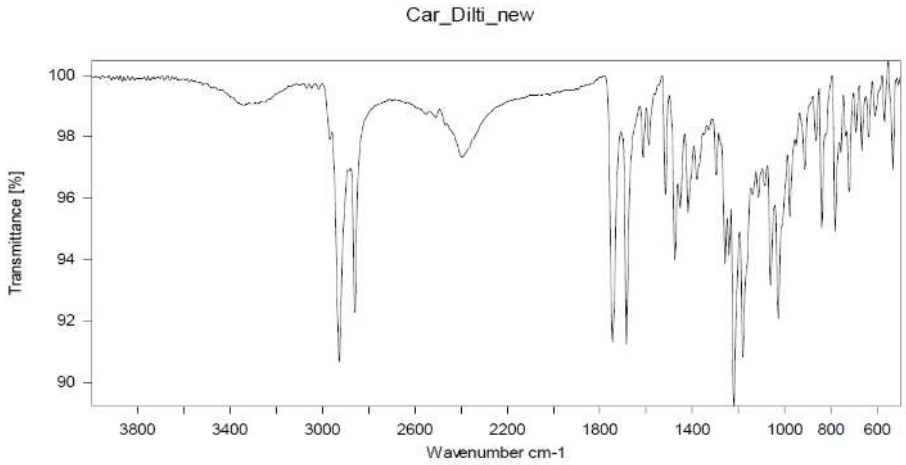


Figure 3: FTIR Spectrum of formulation with carnauba wax

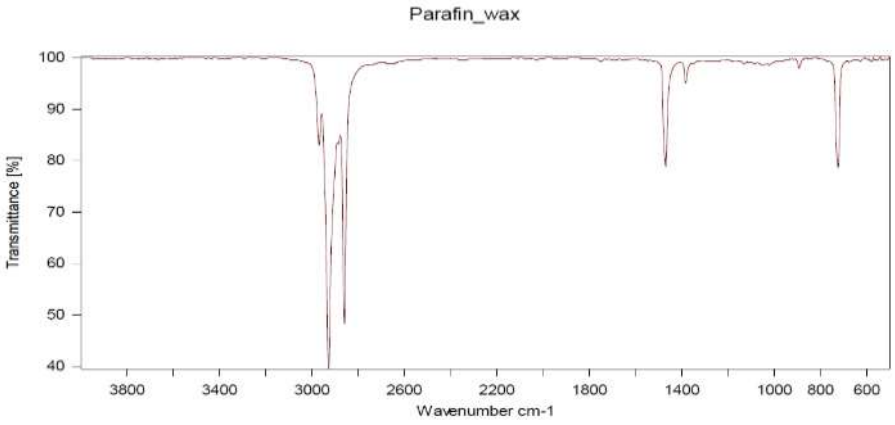


Figure 4: FTIR Spectrum of Paraffin Wax

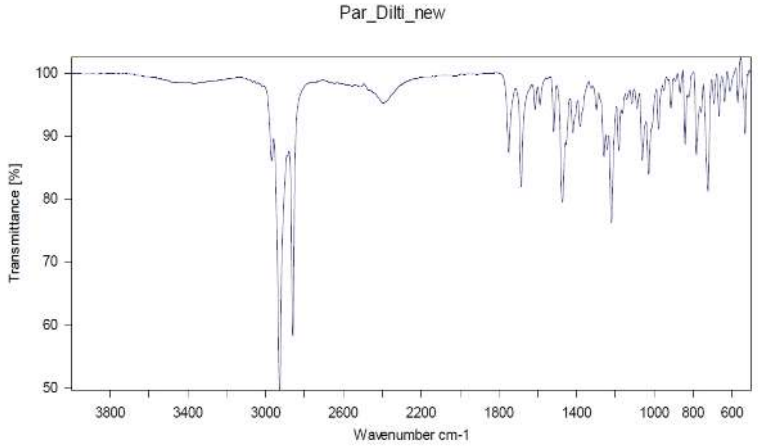


Figure 5: FTIR Spectrum of Formulation with Paraffin Wax

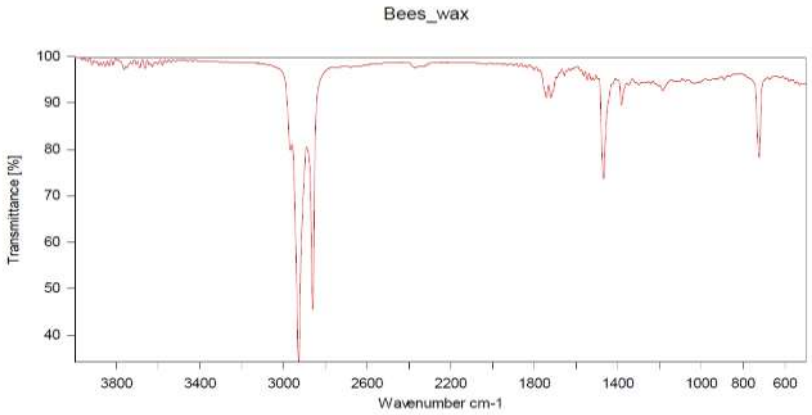


Figure 6: FTIR Spectrum of Bees Wax

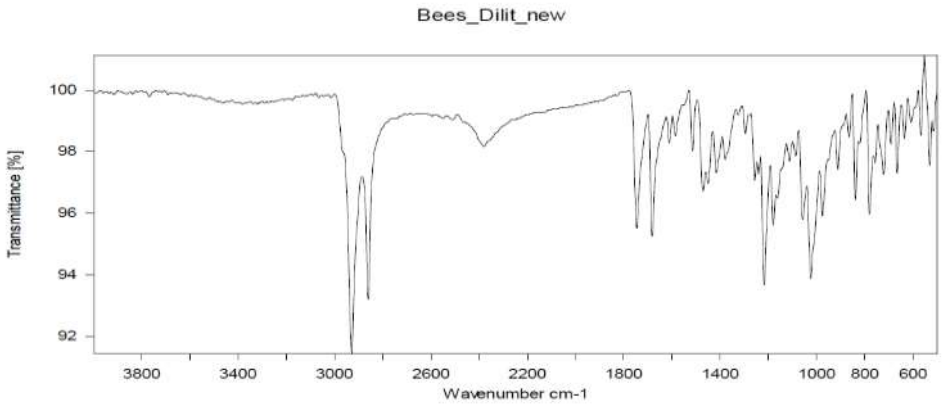


Figure 7: FTIR Spectrum of Formulation with Bees Wax

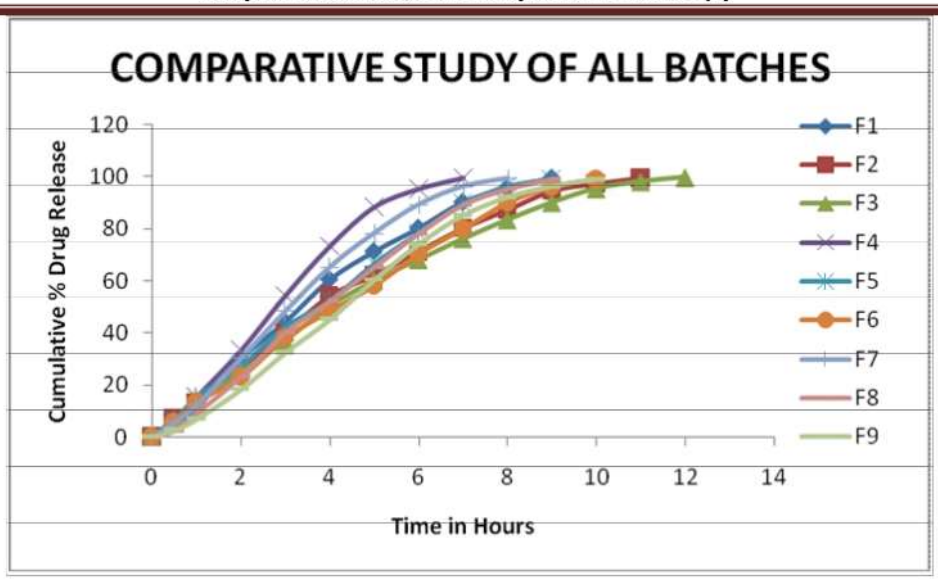


Figure 8: Comparative Drug Release Profile for All Batches

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies by Using FTIR

The drug and excipient compatibility study was done by FTIR method using KBr pellet method.

Characterization of Granules

The blends prepared for compression of tablets were evaluated for their flow properties; the results for Bulk density, Tapped density, Compressibility Index, Hausner's ratio and Angle of repose, were shown in Table 2.

Characterization of Tablets

Tablets were formulated by melt granulation technique and tests such as Weight Variation, Thickness, Hardness, Friability and Drug Content were carried out and results were shown in Table 3.

In-Vitro Drug Release Profile for Formulations

The *in vitro* drug release studies for the prepared formulation were conducted for a period of 12 h using an EDT 08LX dissolution tester USP Type - II apparatus (rotating paddle) set at 100 rpm and a temperature of 37± 0.5°C formulation was placed in the 900 ml of the medium. For first 2 h tablet was placed in 1.2 pH acidic medium which was replaced with 7.4 pH phosphate buffer for remaining 10 h. At specified intervals 5 ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 236 nm for the presence of model drug, using a UV-visible spectrophotometer. Results are shown in Table 4.

Evaluation of Drug Release Kinetics

The optimized formulations were evaluated for drug release kinetics using zero order, first order, Higuchi, Korsmeyer-Peppas model and R^2 values of the formulations were tabulated in the Table 5.

DISCUSSION

In the present study an attempt has been made to prepare sustained release tablet of Diltiazem hydrochloride using different waxes as release retardant polymer by melt granulation technique. The tablets were prepared by melt granulation using different concentrations of waxes such as 30 %, 40 %, 45 %. w/w. Batch F1, F2, F3 contain 35 %, 40 %, 45 % w/w carnauba wax respectively and Batch F4, F5, F6 contain 35 %, 40 %, 45 % w/w paraffin wax respectively and Batch F7, F8, F9 contain 35 %, 40 %, 45 % bees wax respectively. In all formulations concentration of Diltiazem HCl was 36 % w/w.

Drug Excipient Compatibility Study

The drug and excipient compatibility study was done by FTIR method using KBr pellet method in that study it was found that Diltiazem hydrochloride shows characteristic peak at 1748 cm^{-1} shows C=O stretching, 1685 cm^{-1} shows peak for carbonyl group, 1258 cm^{-1} O-H bending and at 784 cm^{-1}. C-H bending and Frequencies of functional groups of pure drug remained intact in physical mixture containing polymers. So it was concluded that there was no major interaction occurred between the drug and excipients used in the formulation. (Figure 1-7)

Physical Characterization of Granules Prepared By Melt Granulation

The granules prepared by melt granulation technique evaluated for characterization such as bulk density, tapped density, hausners ratio, angle of repose, cars index the results are shown in (Table 2) all granules shows good flow property. Bulk density in the range of 0.555 ± 0.001 to 0.720 ± 0.010, Tapped density in the range of 0.642 ± 0.002 to 0.820 ± 0.003, Compressibility index in the range of 12.19 ± 0.84 to 15.82 ± 0.45, Hausnars ratio in the range of 1.13 ± 0.04 to 1.18 ± 0.03, Angle of repose in the range of 27.00± 0.78 to 29.59± 0.62.

Physical Characterization of Tablet Prepared By Melt Granulation

The tablet of Diltiazem HCL (200 mg) prepared by melt granulation evaluated for characterization such as Hardness, Friability, Weight Variation and Content Uniformity the results are shown in (Table 3) all tablets shows sufficient hardness and friability shows that tablets are having sufficient strength. Weight variation is also within range. Friability of all tablets was less than 1 %. Hardness shows in the range of 5.1 - 5.4.thickness in the range of 3.15 -3.25. Weight

variations in the range of 199.58 - 203.20 drug content in the range of 98.76 - 101.00

Dissolution study

From the dissolution study (Table 4) and comparative graph (Figure 8) it was concluded that increase in concentration of wax shows decrease in drug release from tablet. Batch F3 shows 99.84 % drug release at 12 h in comparison with batch F1 and F2 which shows 99.40 % drug release at 9 h and 99.44 % at 11 h respectively. Batch F6 shows 99.23 % drug release at 10 h in comparison with batch F4 and F5 which shows 99.44 % drug release at 7 h and 99.00 % at 9 h respectively. Batch F9 shows 99.24 % drug release at 10 h in comparison with batch F7 and F8 which shows 99.33 % drug release at 8 h and 99.18 % at 9 h respectively. As among all batches batch F3 shows 99.84 cumulative % drug releases at 12 h it was optimized batch.

Drug Release Kinetic Studies

In vitro release data of optimized formulations (Batch F3) was fitted to various kinetic models like zero order, first order, Higuchi, korsmeyer-peppas and pass Higuchi model as it has highest r^2 value (0.955) among all models.

CONCLUSION

In the present study an attempt has been made to prepare sustained release tablet of Diltiazem hydrochloride using different waxes as release retardant polymer. FTIR study shows compatibility between drug and excipients. Pre formulation study shows good flow property of granules prepared by melt granulation. Among all batches Batch F3 shows 99.84 % drug release at 12 h also Batch F3 shows good results of pre formulation study so Batch F3 was best Batch. *In vitro* release data of optimized formulations (Batch F3) pass Higuchi model as it has highest r2 value (0.955) among all models. Sustained release tablets were successfully prepared and evaluated.

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