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RESEARCH ARTICLE

Formulation and Evaluation of Bilayer Tablets of Sustained Release Microspheres of Anti Diabetic Drugs

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ABSTRACT

Diabetes is a major problem worldwide and one of the most common causes for seeking medical consultation. The management of diabetes is a lifelong process, which involves proper planning and control of blood sugar, which should be both uniforms and sustained. Recently multilayer tablets feature more frequently in the design of oral sustained drug delivery systems. These systems consist of an active matrix core and one or more barriers applied during tableting. Bilayer technique will be used to prepare oral extended release dosage form. Bilayer tablets are those with one layer of the drug for immediate release while the second layer designed to release drug, later, either as the second dose or in an extended release manner prepared either by wet granulation/ direct compression/ melt granulation methods etc. The half-life and mean residence time of the drug can be increased by microencapsulation, along with enhanced relative/absolute bioavailability. It can also offer advantages like limiting fluctuation within the therapeutic range, reducing side effects due to a decrease in dosing frequency and improving patient compliance. Therefore, the objective of the present work is to formulate and evaluate bilayer tablets of sustained release microspheres of ant diabetic drugs for the better management of the disease, to minimize side effect as well as to improve patient compliance.

KEYWORDS

Diabetes mellitus, MHCl, PHCl, Microspheres, Bilayer tablets, Direct compression method

INTRODUCTION

The oral route is the most commonly used route for drug administration. Although the different route of administration is used for the delivery of drugs, oral route remain the preferred mode. The oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form[1].

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Introduction to Sustained Release Formulation[2, 3, 4]

For decades an acute or chronic illness is being clinically treated through the delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectable, and suppositories. However, these conventional dosage forms have some drawbacks. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma level of a drug should be maintained within the safe

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margin and effective range. For this proper and calculated doses of the drug need to be given at different time interval by conventional dosage form (Fig. 1.1). To achieve and maintain the concentration of administered drug within a therapeutically effective range, it is often necessary to take drug dosage several times and these results in a fluctuating drug level in plasma.

Mainly greater attention has been focused on the development of controlled or sustained release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms.

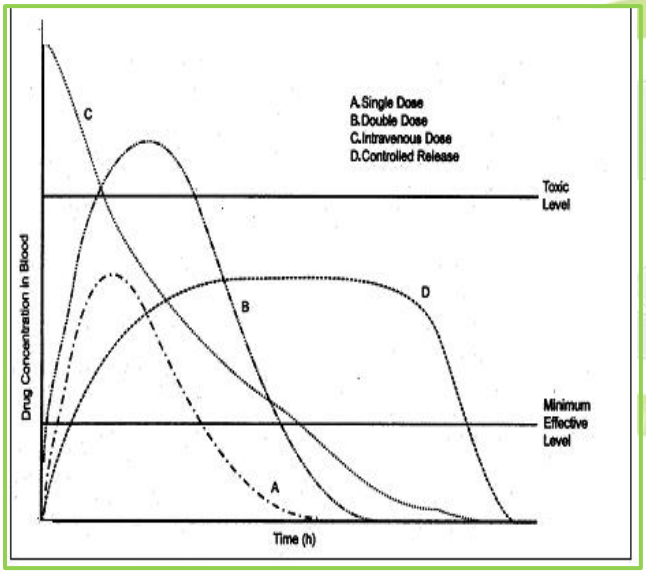

Figure 1: Drug levels in the blood with I.V. administration and Controlled release deliver

Terminologies[5]

- Extended-release dosage form
- Delayed release dosage form
- Modified release dosage form

Microspheres[6]

The term Microsphere is defined as a spherical particle with size varying with diameters in the micrometer range (typically 1µm to 1000µm (1mm), containing a core substance. The microspheres are characteristically free flowing

powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 micrometers. Microsphere has been extensively studied for use as drug delivery systems, where they have been shown to protect sensitive macromolecules from enzymatic and acid degradation, and allow controlled release and tissue targeting of the formulated drug.

Bilayer Tablet[7]

Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives‖. They are also called as Bilayer tablet, multi-layer matrix tablet.

MATERIALS AND METHODS

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. MHCl, PHCl were obtained from Wanbury Ltd., Mumbai. HPMC 15K was obtained from Shreeji chemicals, Mumbai. Acetone, Methanol, Ethanol, Light liquid paraffin oil, Span 80 were obtained from SDFCL Mumbai. Petroleum Ether, Talc, Hydrochloric acid, MCC, Lactose were obtained from Pharma Link Hyderabad. Potassium Dihydrogen Phosphate, Sodium Hydroxide Pellets, Calcium Stearate were obtained from Amishi Drugs and Chemicals Ltd, Ahmedabad.

RESULTS AND DISCUSSION

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in

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developing stable and bioavailable dosage forms, which can be mass-produced.

Identification of MHCl and PHCl

Identification of MHCl and PHCl was carried out by FTIR spectrophotometry.

pH Determination

pH of MHCl and PHCl was determined using potentiometer by digital pH meter.

Melting Point Determination

The melting point of MHCl and PHCl was determined by taking a small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and an average value was noted.

Solubility Studies

An excess amount of the drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. The solution was sonicated and kept at room temp for the attainment of equilibrium. The concentration of MHCl and PHCl of in the filtrate was determined spectrophotometrically by measuring at 233 nm and 269 nm respectively.

Drug Excipient Compatibility Testing

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 400 cm^{-1}. FTIR study was carried out on MHCl, PHCl, Polymer, physical mixture of PHCl and polymer and MHCl and polymer.

Preparation of Standard Calibration Curves

Preparation of Standard Calibration Curves of MHCl

1. **Metformin calibration curve in water at 233 nm**

100 mg of MHCl was dissolved in small amount of water and volume was made up to 100ml using the same. From the stock solution, serial dilutions were done to obtain solutions in the concentration ranging from 10 to 100 mcg/ml. The absorbance of the solution was measured at 233 nm using a UV-visible spectrophotometer. A graph of concentration v/s absorbance was plotted. Similarly, a standard calibration curve of MHCl was prepared in Phosphate buffer pH6.8 and Hydrochloric acid buffer pH 2 by using above said method.

2. **Preparation of Standard Calibration Curve of PHCl at 269nm**

PHCl calibration curve in pH 2 buffer at 269 nm 50 mg of PHCl was dissolved in small amount of water and volume was made up to 100ml using the same. From the stock solution, serial dilutions were done to obtain solutions in the conc. ranging from 10 to 50 mcg/ml. The absorbance of the solution was measured at 269 nm using a UV-visible spectrophotometer. A graph of concentration v/s absorbance was plotted. Similarly, a standard calibration curve of PHCl was prepared in Phosphate buffer pH6.8 and Hydrochloric acid buffer pH 2 by using above said method.

Selection of Directly Compressible Material for Preparation of Bilayered Tablets of MHCl Microspheres and PHCl[2, 8, 9]

The bilayered tablets were prepared by direct compression method. Blends for both layers were prepared separately by weighing and mixing a required quantity of ingredients in geometric proportions for 10 mins. Two different directly compressible materials viz. microcrystalline cellulose and dibasic calcium phosphate were used to compress microspheres to prepare bilayered tablets. The MHCl layer was pre-compressed by hydraulic pellet press by compression force 5 kg/cm^2. Then the PHCl layer was added and the tablet was finally compressed with compression force 25 kg/cm^2 and dwell time 15 secs. The formula for the composition of MHCl layer and PHCl layer is given in Table 1.

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Table 1: Composition of bilayer tablet of MHCl microspheres and PHCl

Ingredient quantity in mg/tablet		MP1		MP2	
		M1	P1	M2	P2
MHCl	PHCl	130	25	130	25
HPMC 15k	HPMC 15k	25	60	25	60
MCC	MCC	100	-	-	40
DCP	DCP	-	40	100	-
Lactose	Lactose	35.5	65	35.5	65
Ca Stearate	Ca Stearate	3.5	6	3.5	6
Talc	Talc	10	4	10	4
Avg. wt. bilayer tablet in mg/tablet		500		500	

Evaluation of Bilayered Tablets of MHCL Microspheres and PHCL [8]

Weight Variation Test

20 tablets were weighed individually, the average weight of tablets was calculated and their upper and lower limits were calculated and Percentage weight variation was calculated using the following formula 1.

$$\text{Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100 \quad \text{----------1}$$

Drug Content

The drug content is determined spectrophotometrically. The tablets were weighed and powdered. An accurately weighed quantity of the sample was taken and extracted in Hydrochloric acid buffer pH 2 and the content was determined using a UV spectrophotometer at 233nm and 269nm. The amount of drug entrapped in the microspheres was calculated using the formula.

$$\text{Drug content} = \frac{\text{Test abs}}{\text{Std abs}} \times \frac{1}{100} \times \frac{100}{\text{Test wt.}} \times \text{dilutions} \times \text{Avg.wt.} \times \frac{100}{\text{Lable claim}}$$

Hardness

The Pfizer hardness tester was used to determine the tablets hardness. The tablets were held between a fixed and moving jaw, the body of the Monsanto hardness tester carrier an adjustable scale which was set zero against an index mark fixed to the compression plunger when the tablets were held between the jaws. The load was gradually increased until the tablets fractured. The value of the load at that point gave a measure of the tablets hardness. Hardness 5 tablets were determined and the average result was tabulated.

Disintegration Time

The test was carried out on 5 tablets using tablet disintegration tester ED-20 distilled water at $37^0C \pm 2^0C$ was used as disintegration media and the time in seconds taken for complete disintegration of the tablets with no palpable

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mass remaining in the apparatus was measured in seconds.

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 20 tablets are deducted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in a formula 2. The weight loss should not be more than 1%.

$$\%\ Friability = \frac{W_0 - W}{W_0} \times 100 \quad \text{.....2}$$

***In vitro* Drug Release Study of Bilayered Tablets of MHCl and PHCl [7, 10]**

In vitro drug release study of bilayered tablets was carried out using USP XXIII basket type dissolution apparatus in two stages.

Stage I :

Medium: pH 2 hydrochloric acid buffer

Time: 2 hours

RPM: 100

Stage II :

Medium: Phosphate buffer pH 6.8.

Time: 10 hours

RPM: 100

Samples of 10 ml each were withdrawn at 1 hr intervals for 12 hours. and analyzed spectrophotometrically at first derivative at 269 nm to determine the concentration of PHCl present in the dissolution medium. And samples were analyzed spectrophotometrically at 233nm to determine the concentration of MHCl in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 10 ml of fresh dissolution fluid after each withdrawal.

Kinetics of Drug Release

The dissolution profile of all the batches was fitted to Zero order, First order and Higuchi to ascertain the kinetic modeling of the drug release. The method of Bamba et al. was adopted for deciding the most appropriate model.

Zero-order

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms (those dosage forms that release the drug in planned, predictable and slower than the normal manner), is zero-order kinetic and can be calculated by formula 3,

$$m = k \times t \text{ .....3}$$

Korsmeyer Peppa's equation:

$$M_t/M_\infty = Kt^n \text{.....4}$$

Where M_t is the amount of drug released at time *t*, M_∞ is the amount of drug released after an infinite time, *k* is a kinetic constant incorporating structural and geometric characteristics of the tablet, and *n* is the diffusional exponent indicative of the drug release mechanism.

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows**:**

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first-order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppa's exponential equation)

Evaluation of Bilayered Tablets of MHCL Microsphere and PHCL

The selection of directly compressible material is critical in case of tableting of microspheres. Two directly compressible materials were taken in the study described in Table 1 and the tablets were evaluated for drug content, hardness, disintegration time, weight variation and

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friability. The results of these tests are shown in Table 3.

Drug Content

The drug content was found to be in the desired limit for all the tablets. MHCl drug content was found to be higher (82.61%) in case of batch MP2 containing DCP as the directly compressible material and batch MP1 containing MCC as directly compressible material showed 81.54% drug release. In case of PHCl content batch, MP2 showed maximum drug content at 94.35%.

Disintegration Time

The disintegration time was found to be higher in case of Batch MP1 was 65 sec. and batch MP2 was found to be 56 sec.

Friability

Friability was found to be less in case of tablets prepared with directly compressible material MCC than DCP.

Hardness

The hardness of all the tablets was found to be around 4-4.1 Kg/cm^2.

***In vitro* Dissolution Study**

The results of the dissolution of bilayered tablets were shown in Table 4 and 5 and Fig. 2. All the tablets showed good release in case of PHCl layer. Batch MP2 were showing the maximum release of MHCl from microspheres layer containing DCP direct compressible material.

Results

Preformulation Studies

Identification

The IR spectrums of pure drugs were found to be similar to the standard spectrum of MHCl and PHCl. The spectrum of MHCl and PHCl shows the following functional groups at their frequencies as shown in Fig. 3 and Table 6.

pH Determination

The pH of MHCl and PHCl was found to be 6.68 and 5.5 respectively.

Melting Point Determination

The melting point of MHCl and PHCl was found to be 222ºC and 188ºC respectively.

Solubility Study

MHCl was found freely soluble in water; soluble in ethanol and methanol; sparingly soluble in chloroform and practically insoluble in acetone. PHCl was freely soluble in N-N dimethylformamide and 5N acetic acid; slightly soluble in ethanol, acetone, and acetonitrile and practically insoluble in water.

Drug Polymer Interaction (FTIR) Study

The results of FTIR study for MHCl, HPMC 15k, a combination of MHCl and HPMC 15k, PHCl, and the combination of PHCl and HPMC

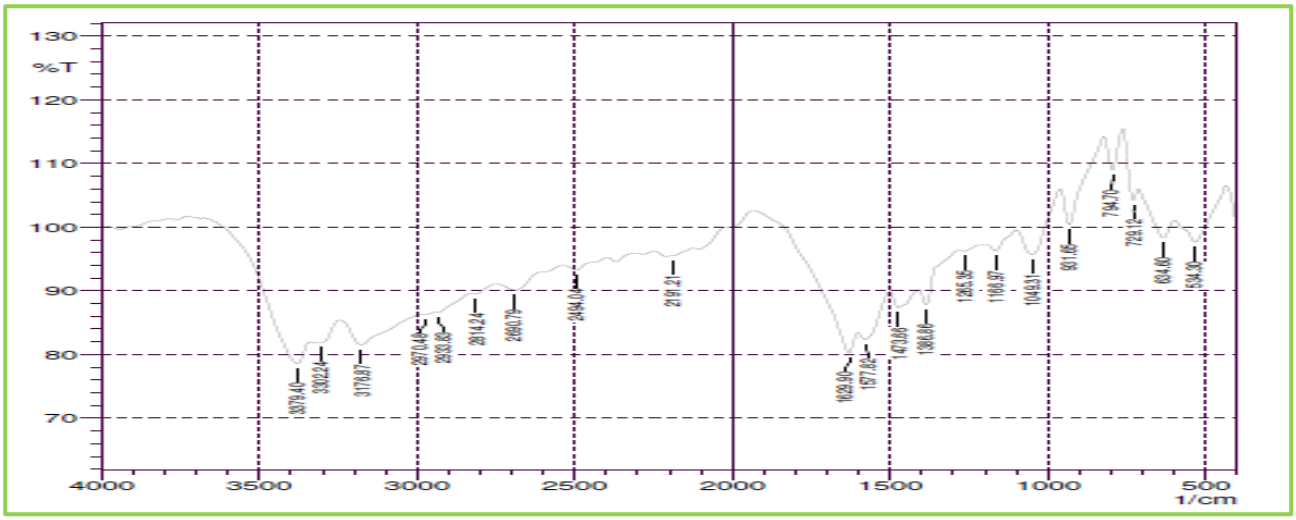

Figure 2: IR Spectrum of MHCl

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Table 2: Results of IR interpretation from spectra

Sl. No.	IR Spectrum	Peaks cm^{-1}	Groups	Stretching / Deformation
1	MHCl	2814.24	C – H	Stretching
		1629.9	C = N	Stretching
		1577.82	N – H	Bending
		1386.86	C – N	Stretching
		729.12	Cl	Stretching
2	Physical mixture of MHCl and polymer	2939.61	C – H	Stretching
		1570.11	N – H	Bending
		1415.80	C – N	Stretching
		1267.27	C – O	Stretching
		3373.61	O – H	Stretching
3	PHCl	2924.18	C – H	Stretching
		1614.47	C = N	Stretching
		1504.53	N – H	Bending
		1390.72	C – N	Stretching
		717.54	Cl	Stretching

Evaluation of Bilayered Tablets of MHCl Microspheres and PHCl

Table 3: Evaluation data of bilayered tablets of MHCl microspheres and PHCl

Batch	Weight variation (mg) mean ±SD (n=10)	Hardness (kg/cm2) (n=5)	Friability (%)	D.T (sec) (n=5)	MHCl content (%)	PHCl content (%)
MP1	500.2±1.48	4	0.87	59	81.54	92.10
MP2	500.4±2.07	4	0.73	63	82.61	94.35

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In vitro dissolution study of bilayered tablets of MHCl microspheres and PHCl

Stage 1: *In vitro* release study for PHCl in pH 2 hydrochloric acid buffer and Phosphate buffer pH 6.8.

Table 4: *In vitro* release data of PHCl layer from bilayered tablets

Sl.No.	Time (min)	% Cum. drug release	
		MP1±SD	MP2±SD
1	0	0	0
2	20	31.66±0.56	43.94±0.47
3	40	41.22±0.88	57.27±0.98
4	60	44.03±1.35	63.03±0.85
5	80	52.58±0.65	76.74±1.20
6	100	77.11±0.75	81.75±1.12
7	120	89.45±1.25	85.02±0.65

Stage 2: *In vitro* release study for MHCl in pH 2 hydrochloric acid buffer and Phosphate buffer pH 6.8.

Table 5: *In vitro* release study

Sl. No.	Time (hrs)	% Cum. drug release	
		MP1±SD	MP2±SD
1	0	0	0
2	1	12.63 ± 0.35	13.16 ± 1.16
3	2	21.92 ± 0.40	26.03 ± 0.98
4	3	28.74 ± 0.80	30.53 ± 0.80
5	4	30.85 ± 0.98	35.71 ± 1.25
6	5	37.76 ± 0.75	41.24 ± 1.30
7	6	43.68 ± 1.20	48.15 ± 0.75
8	7	48.36 ± 0.90	51.58 ± 0.35
9	8	52.29 ± 0.85	56.74 ± 0.45
10	9	57.50 ± 1.12	61.71 ± 0.20
11	10	62.33 ± 1.35	67.37 ± 0.50
12	11	68.18 ± 0.60	72.31 ± 0.65
13	12	70.69 ± 0.75	78.90 ± 1.13

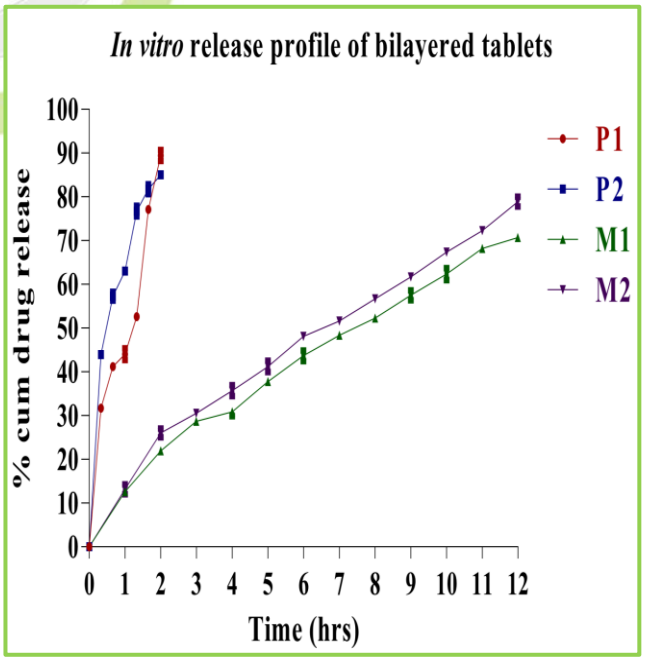

Figure 3: *In vitro* release profile of bilayered tablets of MHCl microspheres and PHCl

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CONCLUSION

The present investigation showed that the HPMC can be used to encapsulate MHCl by a solvent evaporation method. The effect of the drug to polymer ratio was studied and form the results, the following conclusions can be made: On the basis of *in vitro* release studies, E3 was selected as an optimized formulation for designing sustained release formulation. And For further study batch, E3 was used for tableting.

For the immediate release PHCl layer it can be concluded that 4% of the HPMC (batch T2) showed maximum drug release hence batch T2 was selected for further process. Studies on the directly compressible materials revealed that DCP was the best directly compressible material than MCC for compressing of MHCl microspheres. The results of the kinetic study showed that the compressed bilayered tablets followed zero order kinetics and coupling of diffusion and erosion mechanism so-called anomalous diffusion mechanism.

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