CORRELATION BETWEEN COMPACTION AND DISSOLUTION OF METOPROLOL TARTARATE TABLETS PREPARED BY DIRECT COMPRESSION USING DIFFERENT POLYMERS

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ABSTRACT

The investigation is to study the effect of polymers on compressibility and release of Metoprolol Tartarate from tablet through direct compression. Tablets were prepared by direct compression by mixing with commonly used polymers, Eudragit RL-100, Chitosan, Ethyl cellulose, Hydroxyethyl cellulose and hydroxypropylmethyl cellulose K-100 in 1:1 ratio. The compressibility parameters were estimated utilizing Heckel and Kawakita equations. Compactibility, compressibility and tabletibility have been evaluated to understand the total tableting performance. A correlation has been established between 50 % drug release (t50%) and compression bn and chitosan could be utilized for sustained - releasing and fast - releasing agent respectively. Hydroxypropylmethyl cellulose and chitosan are suitable release retardant and fast releasing agents respectively for tablet formulation of Metoprolol Tartarate through direct compression.

Keywords: Metoprolol tartarate tablets.

INTRODUCTION

Choice of excipients is highly important for designing of tablet formulation particularly by direct compression method. Direct compression has several advantages over wet granulation particularly by saving time and money. Choice of binder in designing formulation by direct compression must fulfill certain requirements such as, good binding ability with required drug release and improving better compaction ability of the drug which is particularly poorly compressible[1]. Powder column is a heterogeneous system consisting of solid particles and air. The physical nature of the powder column is different from that of a solid body. During compression process pressure is applied to materials inside the die cavity in between an upper and a lower punch. During compaction of powders, materials lead to volume reduction inside the die cavity. The changes that occur during compression are transitional repacking, deformation at point of contact, fragmentation and/or deformation, bonding, deformation of the solid body, decompression, and ejection[2]. The measurement of porosity changes in a powder column as a function of the compression pressure is a method which is widely used in describing the compaction processes of powders during direct compression. Several equations have been proposed for describing the relationship between the porosity of a powder column and the applied pressure. These equations are also useful for the manufacturing of tablets through directly compressible co-processed micro-granules[3] to improve the compressibility, to increase the clinical effects and bioavailability through pre-gastric absorption[4] and to investigate the compressibility of the granules containing natural crude drug[5]. The objective of this research was to study the basic physico-chemical properties of the commonly used direct compression binders (polymers) and to evaluate the compressibility by studying the porosity-pressure relationship in an attempt to understand, characterize, and compare the binding functionality of these materials. Along with this the release rate of the drug was also studied.

MATERIALS AND METHODS

Materials

The excipients evaluated in this study were purchased from commercial suppliers and used as received. Metoprolol Tartarate was a gift sample from Dr.Reddy's lab.Hydroxypropyl methyl cellulose (HPMC K-100) from MERCK, Ethyl Cellulose from HI-MEDIA, Hydroxyethyl Cellulose from BURGOYNE LAB, Chitosan from HI-MEDIA, and Eudragit RL 100 from MERCK.

COMPACT PREPARATION AND EVALUATION

Compression

Drug polymer mixtures were prepared in 1:1 ratio by mixing 4gm of drug and 4gm of polymer. The mixture (300mg) was directly compressed in different pressure by the help of hydraulic tablet press (model no M-15, Techno search instrument) with one minute dwelling time. All tablets were produced using 10mm diameter, flat-faced, round tooling. Collected tablets were preserved in a screw cap bottle for further studies. Each tablet was weighed accurately, and its diameter and thickness were measured with a digital slide caliper (Digimetric, MDC-25s8). This information was used for the calculation of relative density, porosity and degree of volume reduction, which are essential parameters for Heckel, Kawakita and compaction analysis.

Heckel Analysis

The Heckel equation is described as follows (Equation 1). It is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the densification of the powder bed as the product[6].

$$\ln \frac{1}{1-D} = kP + A$$

(1)

where k and A are constants obtained from the slope and intercept of the plot $\ln(1/(1-D))$ versus P, D is the relative density of a powder compact at pressure P. Constant k (slope) give a measure of the plasticity of a compressed material. Greater slope indicated a greater degree of plasticity of materials. Constant A (intercept) which is extrapolated from the linear part of the Heckel plot. It represents the die filling and particle rearrangement before deformation and bonding of the discrete particles. Thus, a Heckel plot allows for the interpretation of the mechanism of bonding.

Kawakita Analysis

The Kawakita equation (Equation 2) describes the relationship between the volume reduction of the powder column and the applied pressure[7]. The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant.

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad (2)$$

Where, C is the degree of volume reduction of a powder compact at pressure P. The constants (*a* and *b*) can be evaluated from a plot of P/C versus P. A value of *a* is indicative of the maximum volume reduction and describe the compressibility of a powder while *b* is a constant that is inversely related to the yield strength of the particles. The polymer drug mixture was taken in a 25ml measuring cylinder and the cylinder was subjected to tap using a bulk density apparatus. The data from this study were modeled via the Kawakita equation in an attempt to evaluate the relationship between the volume reduction and applied pressure for each studied DC binder.

Hardness

Crushing strength of a tablet was determined by using a digital tablet hardness tester (Campbell electronics, HT-50). Breaking force (F) or crushing strength is a measure of the load at which the tablet breaks under diametrical compression between two flat plates[8], tensile strength is a fundamental measurement of the resistance to fracture[9]. Breaking force can be converted into a tensile strength value, σ, using (equation 3).

$$\sigma = \frac{2F}{\pi dh} \quad (3)$$

Where, *d* is the diameter of the tablet, and *h* is the tablet thickness. The compaction pressure was calculated from the applied force and the cross-sectional area of the punch. The solid fraction (SF) and porosity (ε) were calculated based on the true density (ρ_{true}), tablet volume (*v*), and tablet weight (Wt) as below:

$$SF = \frac{Wt}{\rho true.v} \quad (4)$$

SF is sometimes called relative density. The relationship between SF and ε is shown in eq. 5.

$$\varepsilon = 1 - SF \quad (5)$$

Under the effect of compaction pressure the capacity of a powder to be transformed into a tablet of specified strength known as

tabletability[10]. It is represented by a plot of tensile strength versus compaction pressure. Tabletability describes the effectiveness of the applied pressure in increasing the tensile strength of the tablet. Characterization of the tabletability provides excellent insight into the compaction process and mechanical properties of a material. Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure[10-11]. It indicates the ease with which a powder bed undergoes volume reduction under compaction pressure and is represented by a plot showing the reduction of tablet porosity (i.e., the increase in solid fraction) with increasing compaction pressure. It is also known that tablet porosity is an important parameter, in tablet disintegration and dissolution because some porosity is necessary to improve liquid penetration into tablets. Thus, characterization of the compressibility of a material is also valuable[12-15].Compactibility is the ability of a powdered material to be transformed into tablets with strength during densification. It is represented by a plot of tensile strength versus solid fraction. The compactibility is perhaps the most valuable of the three properties because it reflects the two most important effects of applied pressure: tablet strength and solid fraction. To produce a satisfactory tablet, acceptable tensile strength at an acceptable solid fraction must be produced with the application of pressure. The compactibility of pharmaceutical powders can generally be described by the Ryshkewitch equation[16].

$$\sigma = \sigma_o e^{-b\in} \quad (6)$$

Where σ = tensile strength, σ_{0} = tensile strength at zero porosity, b is a constant, and ε is porosity.

IN-VITRO RELEASE STUDY

All the formulations of prepared tablets of Metoprolol tartarate were subjected to invitro release study. Dissolution is carried out in Electrolab USP dissolution apparatus II (paddle) with a stirring rate of 100 ± 4 rpm. Dissolution medium is 900ml distilled water was taken and maintained at 37º ± 0.5°C Tablet is introduced into the apparatus and sample were withdrawn at appropriate time intervals through a millipore filter up to 10 hours and the drug release was determined using calibration curve at 222 nm. Time required for 50 % of the drug release ($T_{50\%}$) was calculated to compare the dissolution results with the different compression parameters. The results obtained from the release studies were plotted in Peppas-korsmeyer equation and the mechanism of drug release was studied.
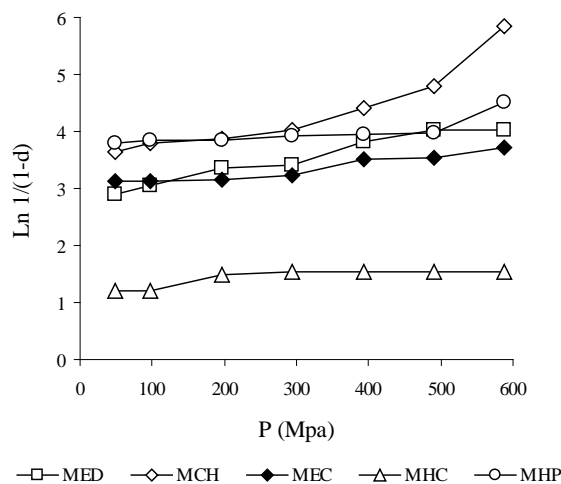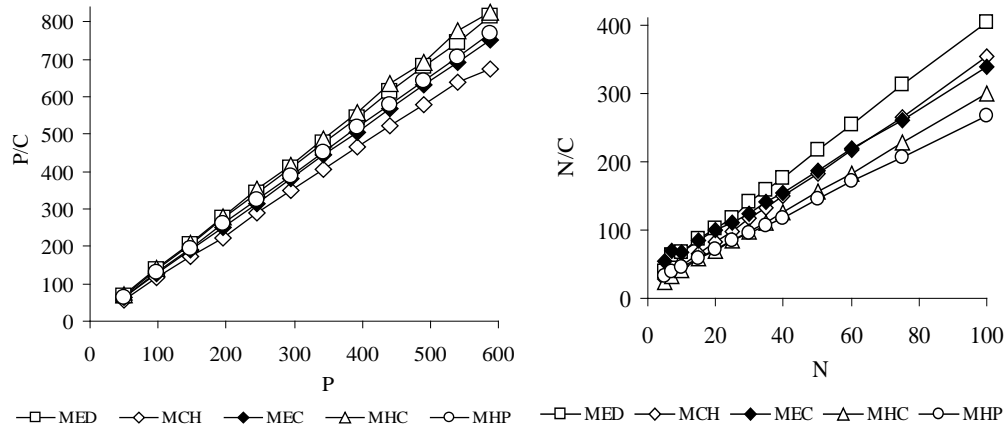
RESULTS

Fig. 1: Heckel plot

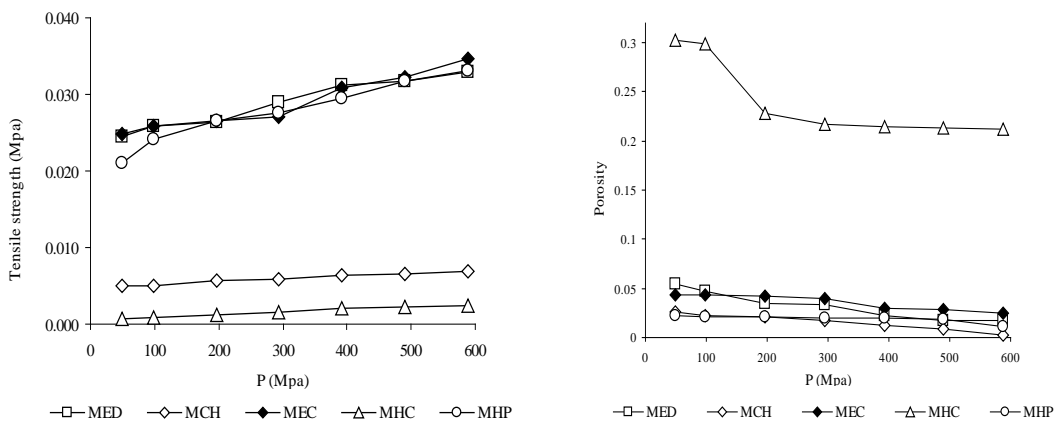**Fig. 2: Kawakita pressure plot and tapping plot**

Fig. 3: Tabletibility profile of the polymers Fig. 4: Compressibility profile of the polymers

Table 1: MED= Drug + Eudragit RL 100; MCH = Drug + Chitosan; MEC = Drug + Ethyl cellulose; MHC= Drug + Hydroxyethyl cellulose; MHP = Drug + Hydroxypropyl methylcellulose k100. a_p and a_t are degree of compression by pressure and tapping respectively; $a_p b_p$ and $a_t b_t$ are rearrangement index by pressure and tapping respectively; K = plasticity; A= Die filling; P_y = yield pressure.

| Formulation	Drug Polymer Ratio	Kawakita Parameters						Heckel Parameters			
		Pressure			Tapping						
		a_p	$a_p b_p$	R^2	A_t	$a_t b_t$	R^2	$K \times 10^{-3}$	P_y	A	R^2
MED	1:1	0.72	0.37	1.0000	0.26	0.04	0.9986	2.24	446	2.84	0.9582
MCH	1:1	0.85	0.44	0.9992	0.30	0.07	0.9998	2.50	400	3.46	0.9380
MEC	1:1	0.77	0.57	0.9999	0.34	0.03	0.9982	1.14	879	3.00	0.9199
MHC	1:1	0.71	0.43	0.9996	0.35	0.08	0.9997	0.16	6165	1.46	0.9582
MHP	1:1	0.76	0.41	0.9999	0.41	0.05	0.9995	0.40	2439	3.78	0.9788
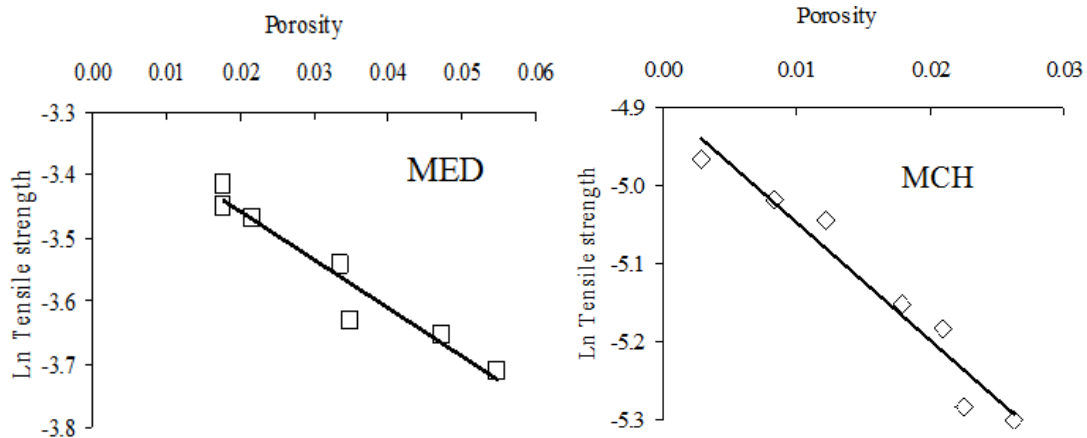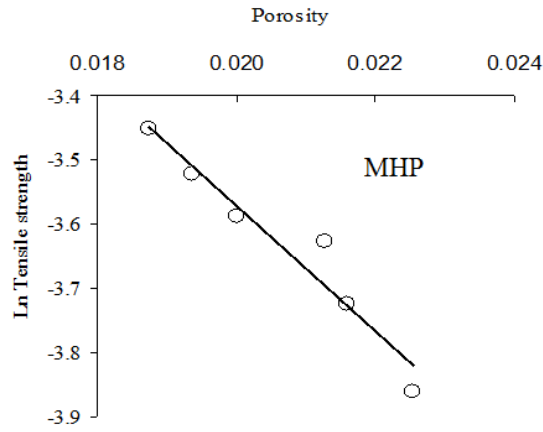
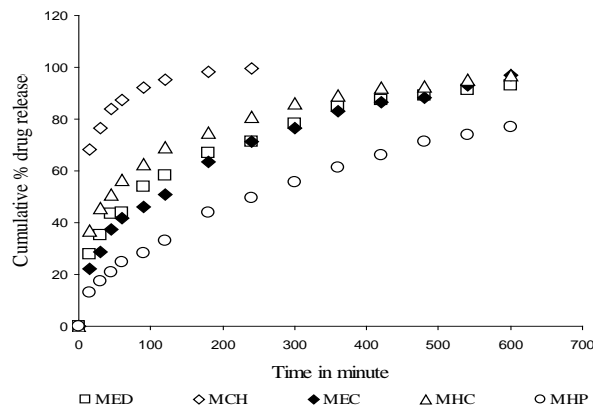**Fig. 5**: **Compactibility profile of the polymers**

Fig. 6: *In-Vitro* **dissolution profile of the tablets of Metoprolol tartarate**
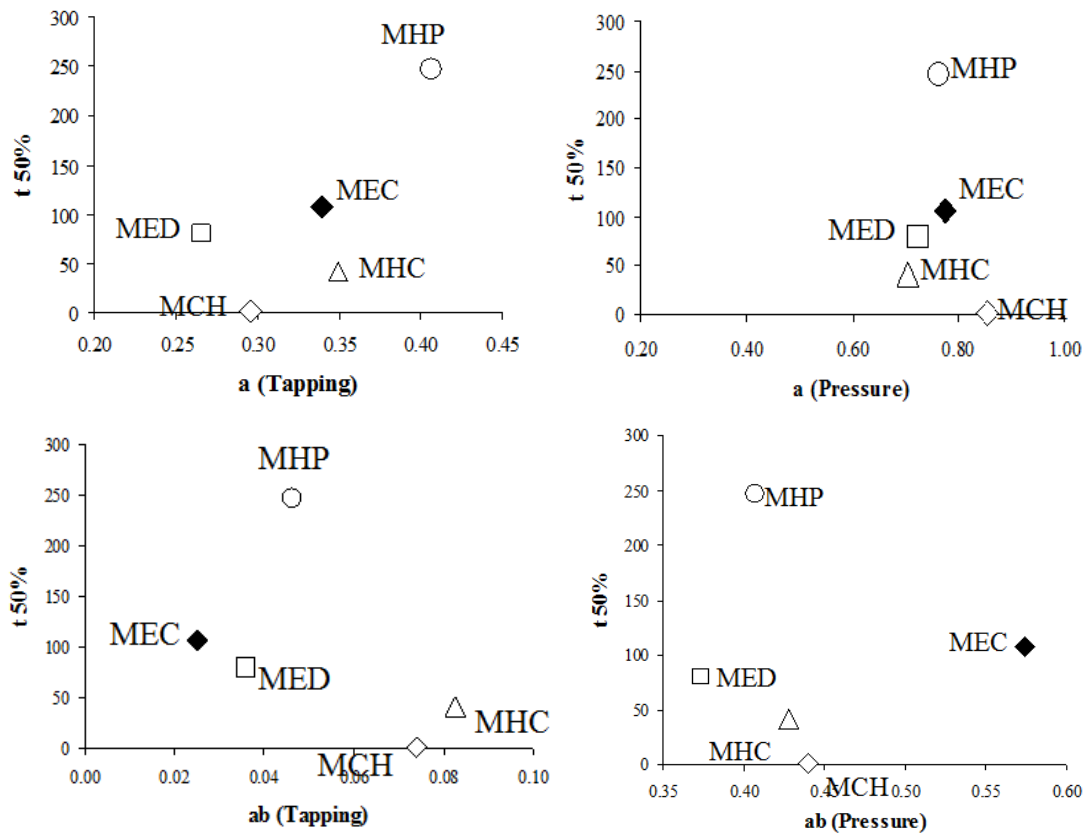

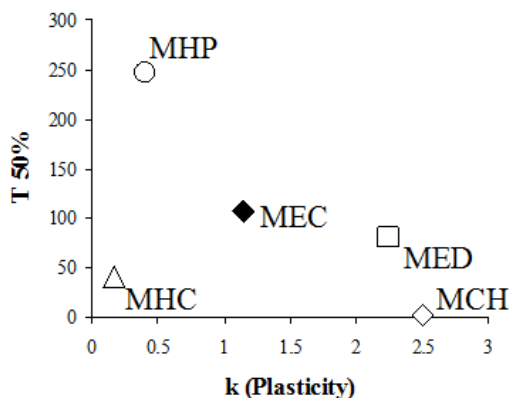**Fig. 7: Correlation plot of T$_{50\%}$ and Kawakita parameters**

Fig. 8: Correlation plot of $T_{50\%}$ and heckle (k) value

DISCUSSION

Heckel Plot

The constants for the Heckel plots of the excipients evaluated in this study are displayed in Table no 1 and figure no 1. The slope of the Heckel plot (k) is indicative of the plastic behavior of the material. A larger value for the slope is related to a greater amount of plasticity in the material. From the study, the plasticity decreases in the following order: Chitosan > Eudragit RL 100, Ethyl cellulose, HPMC K100 and HEC.

Kawakita analysis

The Kawakita constants of polymers from pressure and tapping methods evaluated are listed in Table no 1 and figure no 2. In terms of '*a*' parameter (compressibility) in pressure method, Chitosan exhibited the highest compressibility, followed by Ethyl cellulose, HPMC K100, Eudragit and HEC, whereas in tapping method HPMC K100 exhibited better.

Compaction properties

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure. It is represented by a plot of tensile strength versus compaction pressure. For comparison, the tabletability of all the polymers studied is presented in figure no 3. At the same pressure, HPMC K100 makes the strongest tablets.

Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure. It is represented by a plot of porosity versus compaction pressure. Figure no 4 indicates the reduction of tablet porosity (i.e., the increase in solid fraction) with increasing compaction pressure. From the study it is being observed that the decrease in porosity is more in HPMC K100 compare to other polymers under study.

Compactibility is the ability of a powdered material to be transformed into tablets with strength during densification. It is represented by a plot of tensile strength versus solid fraction. The compactibility is perhaps the most valuable of the three properties because it reflects the two most important effects of applied pressure: tablet strength and solid fraction. The solid fraction increases with decrease in porosity. The compactibility profiles for all the materials studied are shown in Figures no 5. From the plot these results show that polymer HPMC K100 exhibiting low porosity which means more amount of solid fraction.

In vitro drug release studies

Prepared tablets were subjected to drug release study Figure no 6. The results obtained in in-vitro release study were analyzed using in Peppas-korsmeyer equation and found that the release of drug from the tablet prepared with HPMC K100 was by non-fickian diffusion mechanism. A correlation between the Kawakita, Heckel parameters and the time taken for 50% drug release was being established in Figure no 7 and 8.The plot proved that the tablet prepared with HPMC K100 having good sustaining characteristics.

CONCLUSION

Through this investigation different polymers were evaluated for their suitability for direct compression of the drug. By comparing all the finding that the HPMC K100 and chitosan is the polymer of choice in the preparation of sustained release and fast released Metoprolol tartarate tablets through direct compression.

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