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TOWARDS ELUCIDATION OF DRUG RELEASE KINETICS FROM MONOLITHIC HYDROXY PROPYL METHYLCELLULOSE MATRICES CONTAINING RELEASE MODIFIERS.

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ABSTRACT

Hydrophilic and swellable matrices are developed. The developed matrices swellable hydophillic polymer HPMCK100M and various super disintegrants which shows both swelling and gelling property, tapentadol hydrochloride as a model drug which is high soluble water. The prepared tablets were subjected for pre and post compression evaluation. The optimized formulation was showed 12 hours extended release in first order release manner. The effect of superdisintegrant and binder on drug release was clearly distinguished between the formulations. The drug release profile of tapentadol hydrochloride was described by korsemeyer-peppas model better than zero order, first order and hixon-crowell's model, which supports that the release of drug from matrices is regulated by diffusion and erosion mechanisms. From this study, it was elucidated that addition of superdisintegrants and binder can alter the drug release behavior and they may be useful to alter the drug release behavior from polymeric matrices.

Keywords: extended release, monolithic matrices, release kinetics, binder, super disintegrant

INTRODUCTION:

Modified or controlled release oral drug delivery systems have, over the last few decades been shown to offer advantages over conventional systems. These include increased patient compliance selective pharmacological action; reduced side-effect profile and reduced dosing frequency[1, 2]. These systems may therefore have a significantly beneficial outcome in therapeutic efficacy. Controlled release offers prolonged delivery of drugs and maintenance of plasma levels within a therapeutic range. Furthermore, by pairing drug administration rate with drug elimination rate, steady-state plasma levels can be maintained. Currently most drug delivery systems exhibit first-order drug release kinetics where the plasma level of the drug is extremely high after administration and then decreases exponentially[3,4].

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In addition, the polymeric materials used to construct these technologies play an important role in the functioning of these specialized systems. Thus far, various types of polymers have been investigated for their ability to control drug release. Polymers are the essential drug carriers of multilayered matrix tablets and their properties are an important factor in the behavior of these devices[5, 6, 7]. In general, the mechanisms by which polymers perform their functions are by erosion, dissolution and swelling. Some studies have shown that drug release from hydrophilic polymer matrices exhibit a typical time dependent profile in which the drug release is controlled ensuring swelling of the polymer[8, 9].

Preparation of tapentadol extended release matrix tablets:

All the tablets, each containing 100 mg of Tapentadol, were prepared by wet granulation method and also to study the effect of various polymers,binders on the drug release. API, MCC PH 101, croscarmellose sodium, methocel K200M were weighed and mixed for 2 min. The above mixture was passed through sieve # 40. Povidone K30 was dispersed in sufficient quantity of purified water by stirring. Then the above mixture was

granulated using binder solution in rapid mixer granulator. The wet mass was passed through sieve #12. The sieved mixture was dried using FBD and the temperature was maintained at 60°C until the moisture content in the blend comes to 2.0 to 3.5 %. The dried blend was passed through sieve # 20 and then pre lubricated using Aerosil for 20 min and then lubricated with magnesium stearate in blender for 5 min. Then finally the lubricated blend was compressed using 9.5 mm round shape standard concave punches.

Table1: Formulation development of tapentadol extended release tablets using various polymers.

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tapentadol HCL (eq.wt)	116.5	116.5	116.5	116.5	116.5	116.5	116.5	116.5	116.5
MCC PH 101	40	40	40	40	40	40	40	40	40
PVP K30	2	2	6	2	6	6	6	6	6
Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
HPMC K 100 M	55	45	30	32	34	36	38	40	40
Ac-di-sol	-	10	10.4	20	18	16.8	16	13.6	13.6
Plasdone S 630	-	-	14	14.3	15.1	15.5	16	16.5	-
Methocel E 320	-	-	-	-	-	-	-	-	6.3
Colloidal SiO2	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Magnesium Stearate	3	3	3	3	3	3	3	3	3

Evaluation of Pre-compression parameters:

Angle of repose:

The blend was passed through a funnel fixed to a burette stand at a height of 4 cm. A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where, h = Height of the pile,
r = Radius of the pile

Tapped density:

It was measured by transferring a known quantity (25 gms) of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

$$\text{Tapped density} = W/V_f \text{ g/ml}$$

Where, W= Mass of the blend, V_f = tapped volume

Compressibility index (carr's index):

Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

Percentage compressibility = [(Tapped density – Bulk density)/Tapped density] X 100

Evaluation parameters of tablets:

Weight variation test:

Twenty tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

$$\% \text{ weight variation} = ((A-B)/B) \times 100$$

Where,
A = Average weight of tablets,
B = Individual weight of tablet

Hardness:

The hardness test is performed to measure the tablet strength. Tablet should be hard enough to withstand packing and shipping. Electro lab hardness tester was used for the determination of hardness of tablets. The hardness of 10 tablets was noted and the average hardness was calculated. It is expressed in kp or kg/cm^2.

Thickness:

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter.

Friability:

The friability test gives an indication of tablets ability to resist chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets friability value of 1.0% or less is desirable. If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. The tablets were rotated in the Roche friabilator for 100 revolutions at 25 rpm and then de-dusted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\text{Percentage friability} = ((A-B)/B) \times 100$$

Where, A = Initial weight of tablets
B = Final weight of tablets after 100 revolutions

Assay:

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount. Six tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average

weight of three tablets of Tapentadol hcl was transferred to a 100ml volumetric flask containing 6.8p^H Phosphate buffer solution and the volume was made up to the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it was filtered through whatman filter paper. From this resulted solution 1ml was taken, diluted to 10ml with 6.8 p^H phosphate buffer solution and absorbance was measured against blank at 279 nm[9].

Dissolution study

The dissolution test measures the rate of release of the drug from the dosage form *in vitro*, it is usually expressed as extent of dissolution (% drug content) occurring after a given time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug into the surrounding medium plays a vital role. Though dissolution is not a predictor of therapeutic efficacy it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form. For conduction of dissolution studies USP Type-II (Paddle) was used. Dissolution conditions were 900 ml pH 6.8 Phosphate buffer maintained at 37±0.5^{o}C and paddle speed 75 rpm maintained. Samples were collected 0.5, 2, 4, 6, 8, 10, 12hours time points and drug content was estimated spectrophotometrically.

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Stability studies were conducted according to ICH Guidelines; the optimized formulation was packed in Al-Al blisters and stored at accelerated conditions in a stability chamber for a period of 3 months. The samples were evaluated for assay and dissolution studies at regular intervals[10-12].

RESULTS AND DISCUSSION:

Calibration Curve of Tapentadol Hydrochloride in phosphate buffer pH 6.8.

The standard calibration curve of Tapentadol Hydrochloride in 6.8 phosphate buffer solution was developed in the concentration range of 50 – 250 µg/ml with suitable dilutions of same medium and aliquots are observed for their absorbance under UV- spectrophotometer at an absorption maximum of 279 nm. The standard graph of Tapentadol hydrochloride has shown good linearity with R^2 value 0.999 in pH 6.8 buffer (Figure 1) , which suggests that it obeys the "Beer-Lambert's law.

Evaluation of Precompression parameters:

The precompression evaluation was done as per the methods depicted above. The Precompression blend for tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and all the formulations were found to show very good results for the above evaluation parameters. Compressibility index of all the formulations was found in between 12 to 15, indicates good compressibility index. Angle of repose of all formulations are found to be < 30º C, declares that all the formulations are possessing good flow properties and Hausner's ratio of all formulations was found to be less than 1.25, which satisfies the limits of compressibility. The results were showed in table no.2.

Evaluation of post compression parameters:

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 2. All the tablets of different batches complied with the official requirements of weight variation as their weight variation passes the limits . The hardness of the tablets ranged below 15 kg/cm^2 and the friability values were less than 0.5% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 5.1±.02 mm. All the formulations satisfied the content of the drug as they contained 95 to 102 % of Tapentadol and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.All formulations (n = 5) were tested for physical parameters like hardness, thickness, weight variation, friability and found to be within the Pharmacopoeial limits.

Dissolution studies:

The results were mentioned in table 3. From results, we observed that change in binder and addition of superdisintegrant to HPMC matrices showed a significant impact on drug release and release pattern. Dissolution profile of all formulations was compared. In F1 and F2 formulations the drug release was not complete as per specified time duration. The percentage drug release at the end of 12h was 74.5%, 80.2% for formulations F1 and F2 respectively. In formulations F3 to F6 the drug release was found to be 76.8%, 79.9%, 81.4%, 85.5%.Drug release was increased but not upto the mark. Formulation F7 was observed to have the desired drug release profile by increasing the polymer concentration.The drug release was found to be 91.5% at the end of 12th hour in case of F7 formulation. Formulation F8 was observed to have drug release of 95.2% at the end of 12h by increasing the polymer and binder concentration with varying amounts of disintegrant.

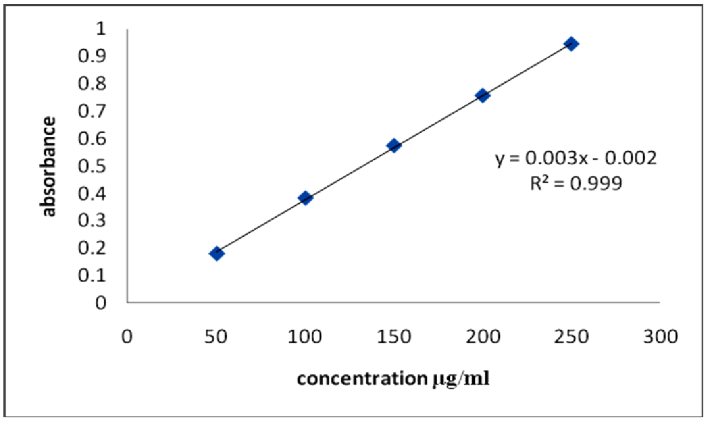


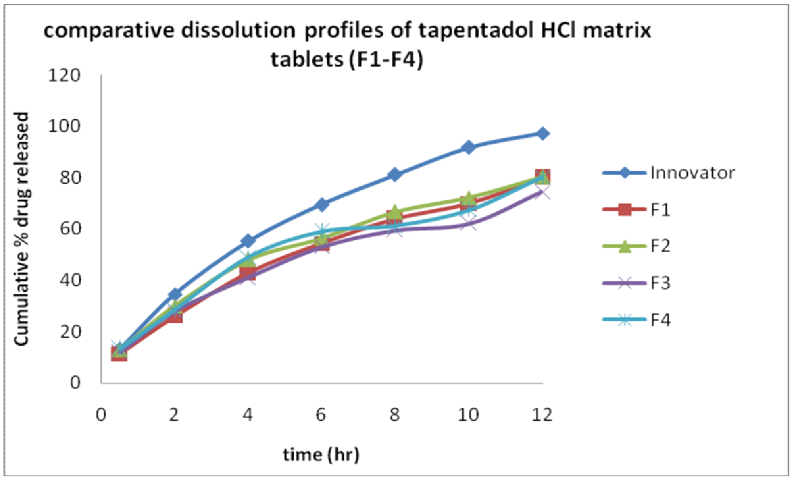
Fig 1: Calibration Curve of Tapentadol Hydrochloride in pH 6.8 phosphate buffer.

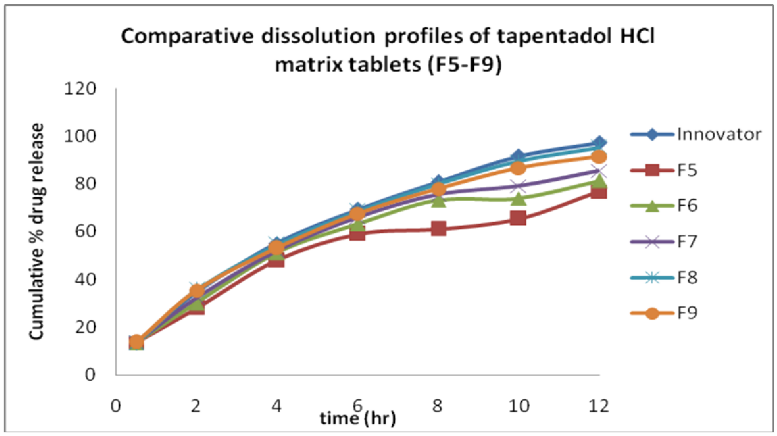
Table 2: precompression parameters of powder blend for formulations

Parameter	Angle of repose(°c)	Bulk density	Tapped density	Hausner's ratio	Compressibility index
F1	25.43±0.64	0.725±0.01	0.829±0.01	1.14	12.54±0.28
F2	26.46±1.10	0.7340±0.02	0.854±0.03	1.16	14.05±0.22
F3	27.31±1.36	0.717±0.03	0.832±0.02	1.16	13.82±0.33
F4	23.29±0.40	0.724±0.03	0.843±0.02	1.16	13.63±0.75
F5	29.14±0.50	0.703±0.02	0.815±0.02	1.15	13.74±0.51
F6	24.54±0.20	0.719±0.02	0.835±0.02	1.16	13.89±0.49
F7	26.56±0.76	0.713±0.02	0.826±0.01	1.15	13.68±0.38
F8	26.49±0.68	0.701±0.01	0.814±0.02	1.16	13.88±0.42
F9	25.43±0.62	0.702±0.04	0.824±0.04	1.15	13.78±0.22

Table 3: post compression evaluation results of prepared tapentadol HCl matrix formulations

Formulation	***Weight variation (mg)**	****Thickness (mm)**	****Hardness (kg/cm^2)**	**Friability(%)**	*****Drug content (%)**
F 1	222.3±1.02	4.1±.03	6.2±0.3	0.12%	99.01%
F 2	223.1±0.91	4.1±.04	6.8±0.3	0.16%	101.4%
F 3	225.9±0.99	4.1±.06	7.3±0.2	0.15%	99.35%
F 4	233.8±0.21	4.2±.04	6.8±0.2	0.15%	98.41%
F 5	238.8±1.21	4.4±.02	6.7±0.6	0.15%	99.51%
F 6	240.1±1.36	4.2±.02	6.7±0.7	0.15%	99.37%
F 7	241.8±0.98	4.0±.05	7.2±0.1	0.15%	100.5%
F 8	224.7±0.87	4.2±.06	6.5±0.4	0.15%	100.1%
F9	224.7±0.87	4.2±.03	6.5±0.4	0.15%	100.1%





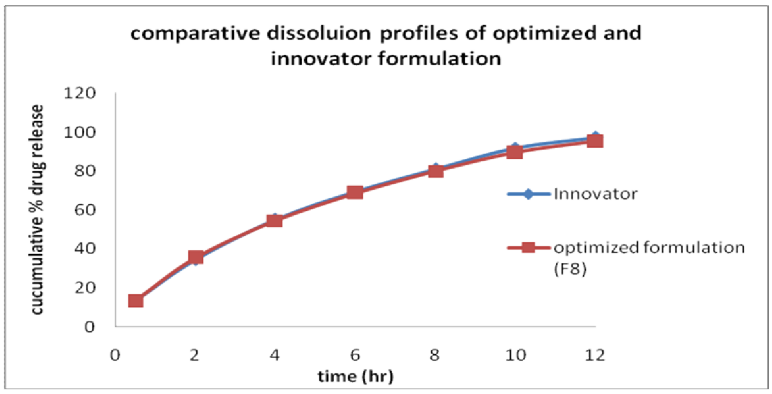


Fig 2: Comparative dissolution profiles of prepared extended release matrix tablets and Innovator

Formulation code	Zero order	First order	peppas		Higuchi model
			R^2	n value	
F1	0.9278	0.9789	0.9967	0.5683	0.9892
F2	0.9299	0.9767	0.9950	0.5693	0.9933
F3	0.9119	0.9650	0.9874	0.5572	0.9869
F4	0.9004	0.9644	0.9860	0.5490	0.9857
F5	0.9053	0.9773	0.9884	0.5682	0.9886
F6	0.9016	0.9793	0.9884	0.5806	0.9870
F7	0.9116	0.9935	0.9915	0.5931	0.9912
F8	0.9281	0.9960	0.9940	0.6060	0.9956
F9	0.9352	0.9776	0.9940	0.6258	0.9956
INNOVATOR	0.9409	0.9530	0.9957	0.6353	0.9946

Table 4: release kinetics studies on dissolution studies of prepared formulations

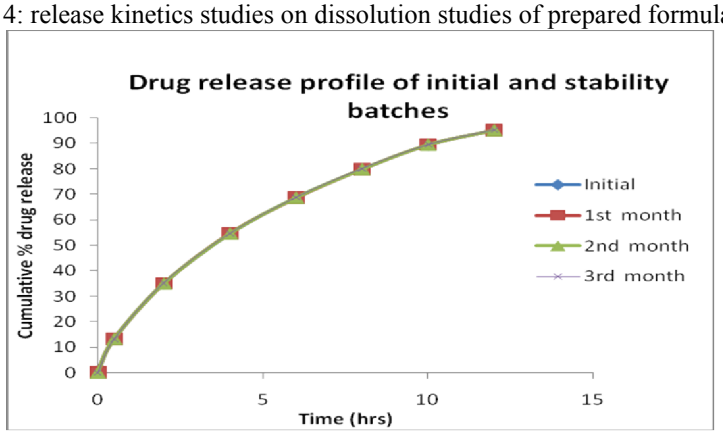


Fig 3: Dissolution profiles of initial and stability batches (samples collected at 1st, 2nd and 3rd month)

Release kinetics:

All prepared formulations were checked for the model fitting. These formulations were checked for zero order, first order, Higuchi and Kosmeyer-Peppas equation. Among all trials, the drug release was found to be for the formulations F8 has release profile which was similar to the innovator release profile. So formulation F8 was selected for further studies like kinetic data analysis.

The optimized formulation was checked for the model fitting. The optimized formulation shown the zero order $R^2 = 0.935$, first order $R^2 = 0.977$, Higuchi $R^2 = 0.995$.As shown in Figure drug release data was best explained by first order equation, as the plots showed the highest linearity ($r^2 = 0.997$) and Higuchi's equation ($r^2 = 0.995$). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The formulation F8 drug release profile matches with the innovator drug release profile.

Stability studies:

The optimized tablets from batch F8 were charged for stability studies at 40^0C and 75% RH. There was no change in physical appearance, color. Formulations were analyzed at the end of 3 months for general tablet properties like hardness, friability, drug content and dissolution studies. Tablets have shown not shown deviation in hardness, friability values and drug content. In vitro dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of 3 months.

CONCLUSION:

In the present study an attempt was made to prepare extended release tablets of Tapentadol Hydrochloride and compose the same with that of marketed product. From the experimental results it can be concluded that, extended release Tapentadol Hcl tablets can be prepared by wet granulation method using different polymers in varying percentages. Formulation F8 containing HPMC K100M as rate controlling polymer was chosen as the optimised formulation, based on the parameters evaluated. Formulation F8 containing high percentage of HPMC K 100 M was found to be optimized formulation as it released 95.2% drug in 12 hrs. However it needs further in depth in-vivo release studies on suitable animal models with statistical clinical data for a dependable and successful pharmaceutical marketing formulations.

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